Novel Paradigms in Cancer That May Lead to Better Therapies

Mauricio Burotto, MD
Medical Oncology
National Cancer Institute
National Institutes of Health

1960 - 1970's

Exciting times with chemotherapy effecting tumor shrinkage in lymphoma.
In Building 10, DeVita gives a combination of four drugs to a patient with Hodgkin's for a first time.

But comparing therapies emerges as an important goal

Where did the definition of partial response [PR] come from?

Charles G. Moertel, MD
[1927 – 1994]

1976
16 oncologists
12 spheres
1920 measurements

Where did the definition of PR come from?

Twelve solid spheres were selected, measuring from 1.8 to 14.5 cm in diameter. It was assumed that this size range would cover the sizes usually encountered in measurable clinical masses such as subcutaneous, lymph node, and intra-abdominal tumors. These masses were then arranged in random size order on a soft mattress and covered with a layer of foam rubber. This layer measured 0.5 in. in thickness for the six smaller masses to approximate skin and subcutaneous tissue and 1.5 in. for the six larger masses to approximate abdominal wall. Each of 16 experienced physicians practicing in oncology was then asked to measure the diameter of each sphere using the usual technique and equipment (ruler or caliper) he employed in clinical practice.

Where did the definition of PR come from?

The actual "tumor" diameters are shown in Table 1. The participants were unaware that "tumors" 5 and 6 were designed to have the same diameter and so to provide an estimate of the reproducibility of each physician's measurements of tumor size. Tumors 7 and 8 were also designed for this purpose (the slight difference in true diameters 5 and 6 and in 7 and 8 reflect variations in the manufacturing process).

Where did the definitions of response come from?

How often did two different investigators think the same tumor was actually different?

No. of pairings who report objective responses	
≥ 25% shrinkage	≥ 50% shrinkage
29	6
70	26
60	8
83	39
57	7
64	18
51	7
65	19
479 (24.9%)	130 (6.8%)

How often did the same investigators think the same tumor was actually different?

No. of investigators who reported objective responses	
≥ 25% shrinkage	≥ 50% shrinkage
4	4
2	0
3	1
3	0
12 (18.8%)	5 (7.8%)

THE EFFECT OF MEASURING ERROR ON THE RESULTS OF THERAPEUTIC TRIALS IN ADVANCED CANCER

CHARLES G. MOERTEL, MD,* AND JAMES A. HANLEY, PHD†

In this study, 16 experienced oncologists each measured 12 simulated tumor masses employing their usual clinical methods. Unknown to the oncologists, two pairs of these tumors were identical in size. This permitted a total of 64 measurement comparisons of the same investigator measuring the same size mass and 1920 comparisons of different investigators measuring the same size mass. If a 50% reduction in the product of perpendicular diameters is accepted as a criterion, the objective response rate due to measuring error alone was 7.8% by the same investigator and 6.8%by different investigators. If a 25% reduction criterion is used, the respective "placebo" response rates were 19% and 25%. In the clinical setting it is recommended that the 50% reduction criterion be employed and that the investigator should anticipate an objective response rate of 5 to 10% due to human error in tumor measurement.

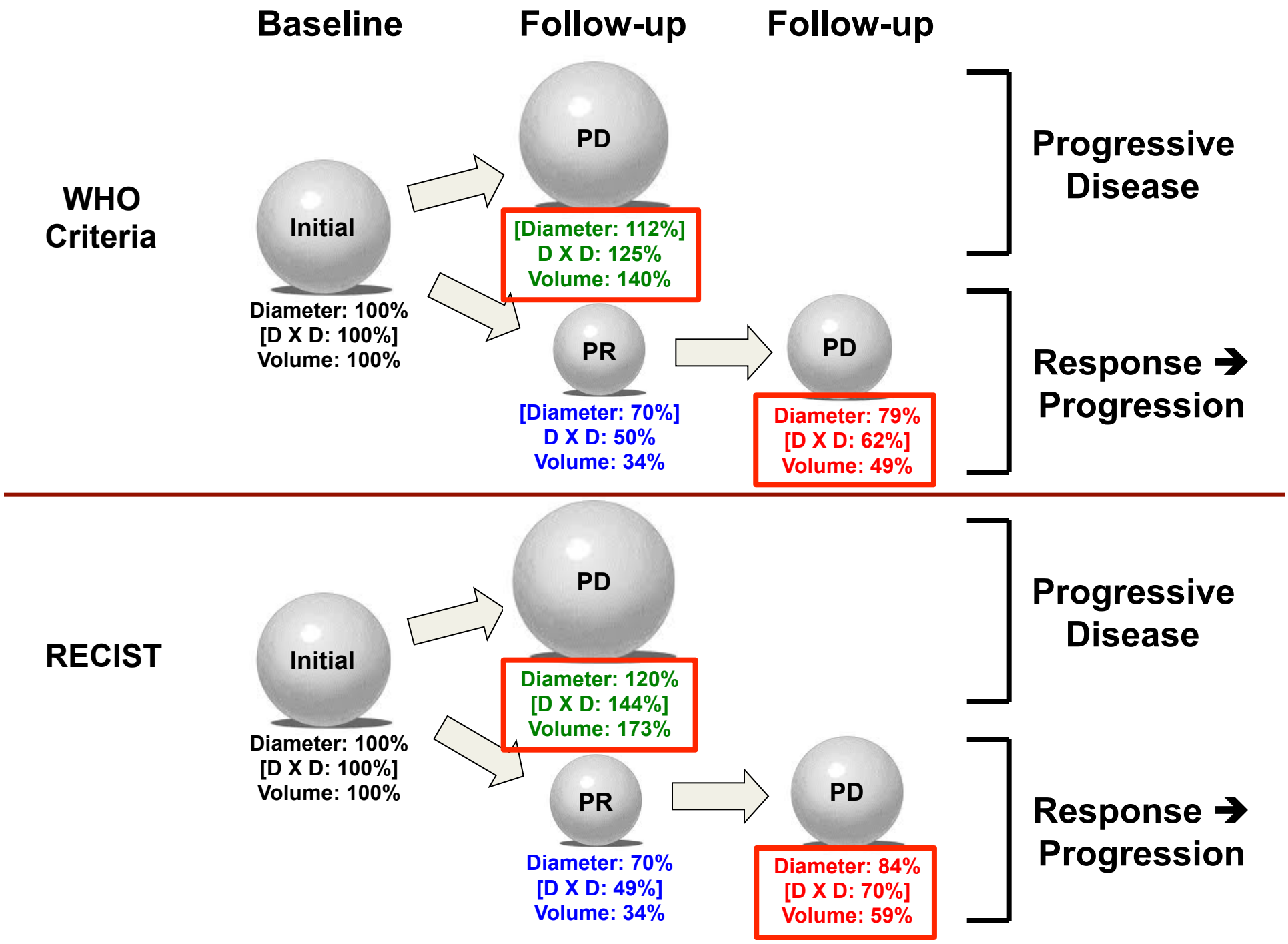
Cancer **38:388–394, 1976.**

From these humble beginnings….from cutoffs chosen for "operational reasons" not for "efficacy"….we evolved to assessment of efficacy

Response Rate

WHO
(**W**orld **H**ealth **O**rganization)
versus
RECIST
(**R**esponse **E**valuation **C**riteria **I**n **S**olid **T**umors)

	WHO	RECIST
Measurability	Measurable, bidimensional	Measurable, unidimensional: Conventional method ≥20 mm; Spiral CT ≥10 mm; Target versus non-target lesion
	Non-measurable/evaluable	Non-measurable
Objective response		
Complete response (CR)	Disappearance of all known lesion(s); confirmed at 4 weeks	Disappearance of all known lesion(s); confirmed at 4 weeks
Partial response (PR)	At least 50% decrease; confirmed at 4 weeks	At least 30% decrease; confirmed at 4 weeks
Stable disease (SD)	Neither PR nor PD criteria met	Neither PR nor PD criteria met
Progressive disease (PD)	25% increase; no CR, PR or SD documented before increased disease, or new lesion(s)	20% increase; no CR, PR, or SD documented before increased disease, or new lesion(s)

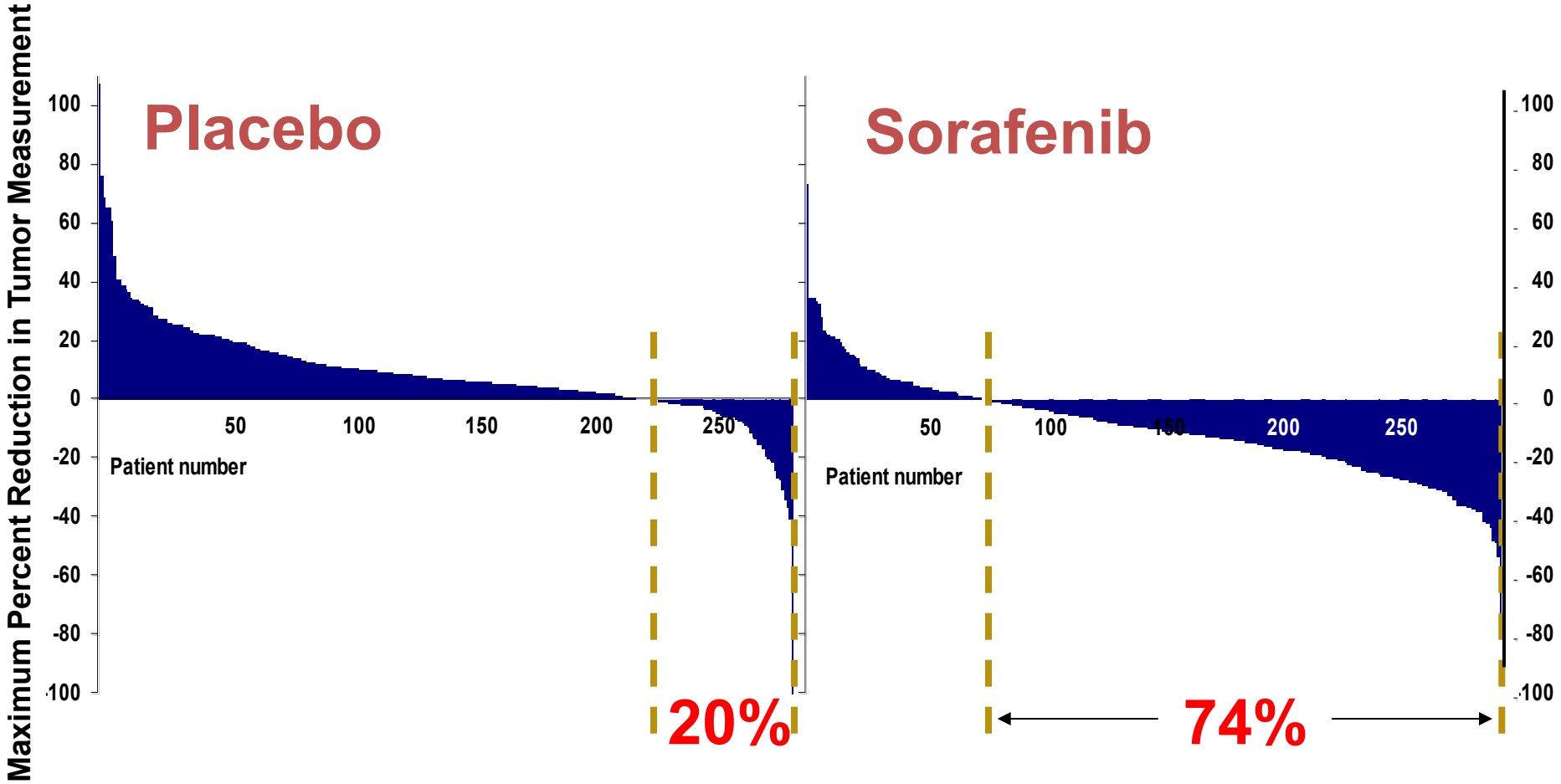

Baseline
Follow-up
Follow-up
WHO Criteria
Initial
Diameter: 100%
[D X D: 100%]
Volume: 100%
PD
[Diameter: 112%]
D X D: 125%
Volume: 140%
PR
[Diameter: 70%]
D X D: 50%
Volume: 34%
PD
Diameter: 79%
[D X D: 62%]
Volume: 49%
Progressive Disease
Response ➔ Progression
RECIST
Initial
Diameter: 100%
[D X D: 100%]
Volume: 100%
PD
Diameter: 120%
[D X D: 144%]
Volume: 173%
PR
Diameter: 70%
[D X D: 49%]
Volume: 34%
PD
Diameter: 84%
[D X D: 70%]
Volume: 59%
Progressive Disease
Response ➔ Progression

It’s been 37 years since Moertel and Hanley
Should we be thinking about different ways of assessing efficacy?
Probably

But…

Sorafenib in RCC (TARGET Trial)
A Disease-Stabilizing Agent?

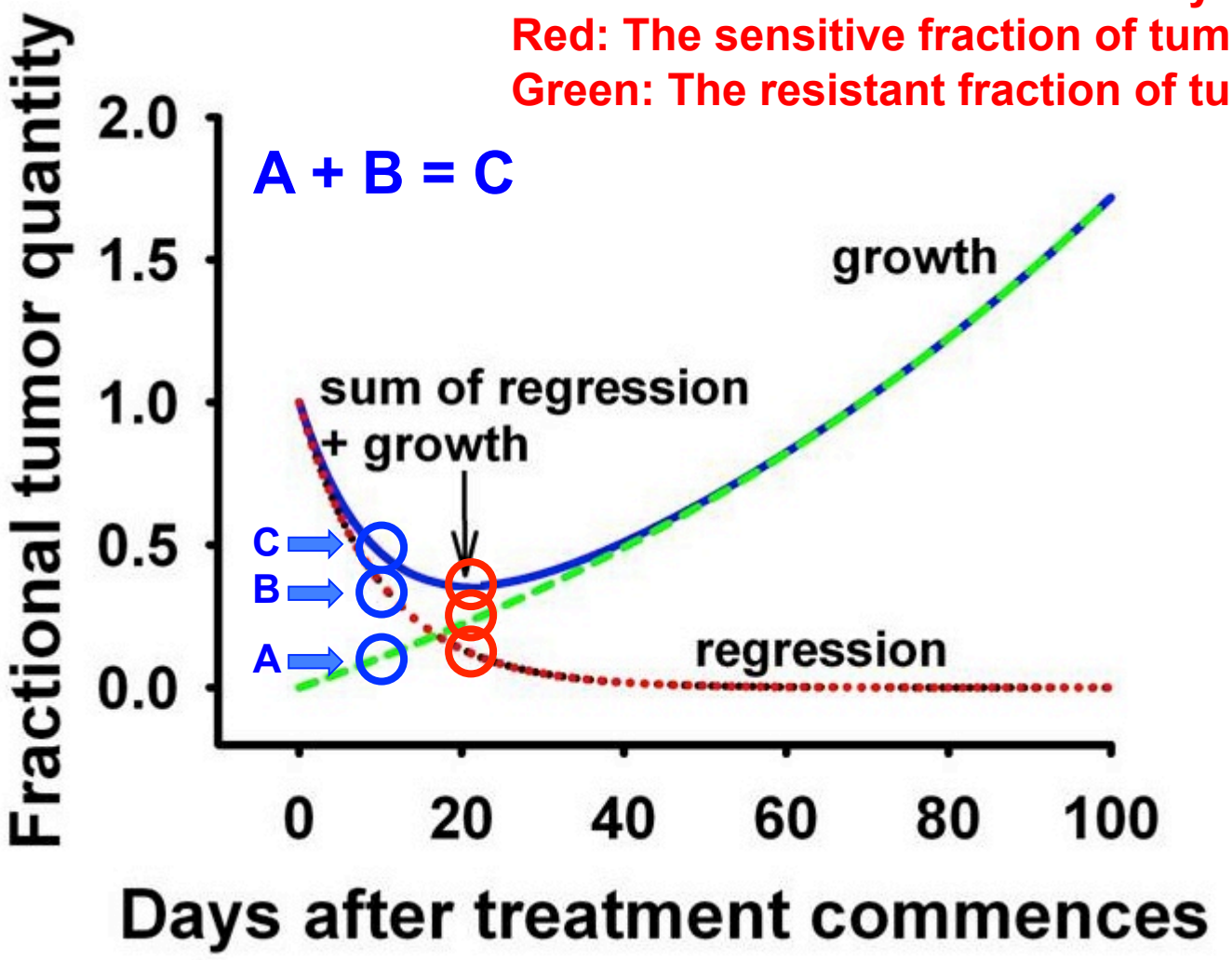
This presented a challenge: Could we better evaluate efficacy?
Could we better measure the effect of drug on tumor growth?



*Independently assessed measurements available for 574 patients

Theory for regression and growth

Blue: What we measure clinically
Red: The sensitive fraction of tumor regressing
Green: The resistant fraction of tumor growing



$$f = e^{(-d \cdot t)} + e^{(g \cdot t)} - 1$$

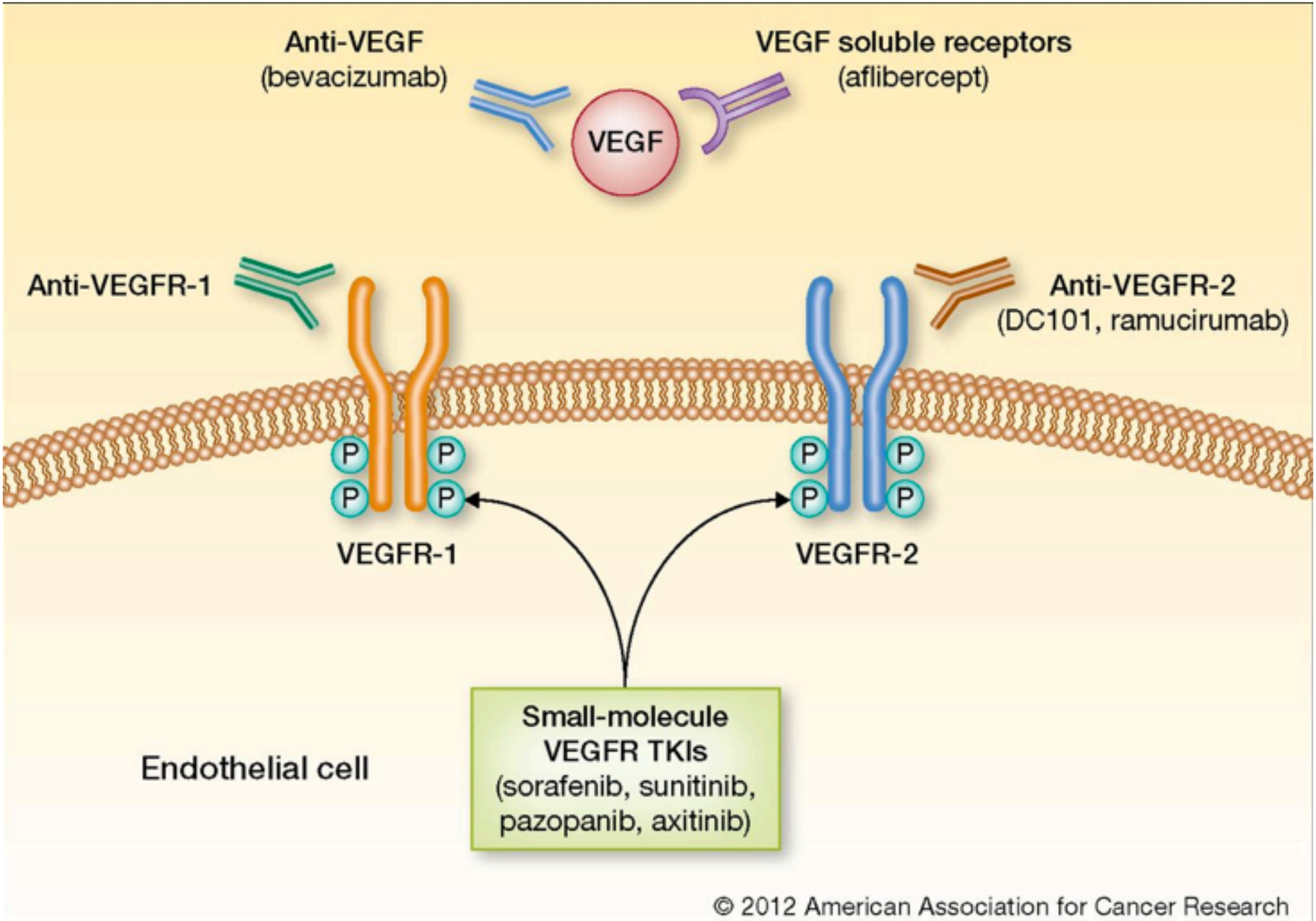
Where f = tumor measurement in t days
d = regression rate constant; g = growth rate constant

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 31, 2003 VOL. 349 NO. 5

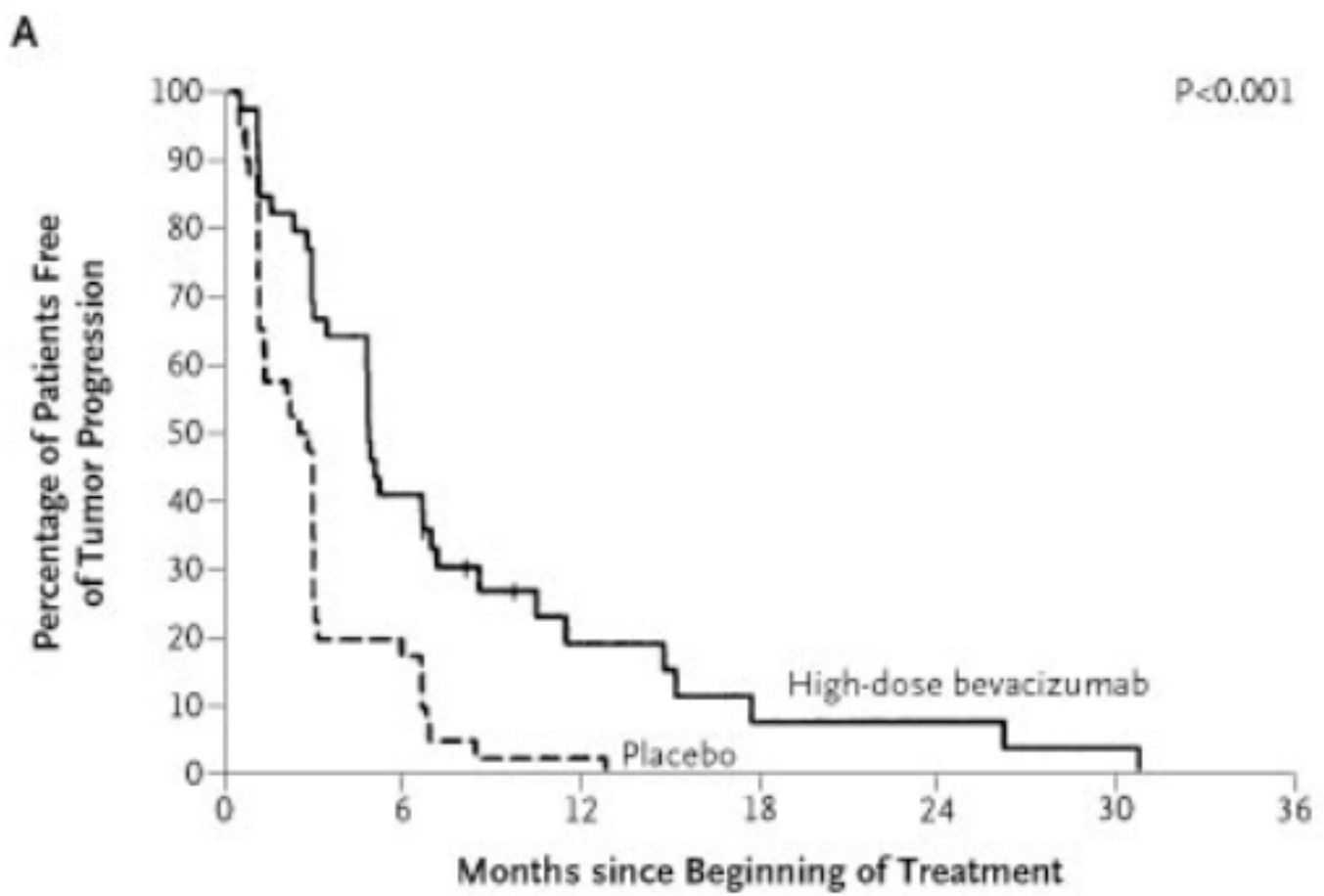
A Randomized Trial of Bevacizumab, an Anti–Vascular Endothelial Growth Factor Antibody, for Metastatic Renal Cancer

James C. Yang, M.D., Leah Haworth, B.S.N., Richard M. Sherry, M.D., Patrick Hwu, M.D., Douglas J. Schwartzentruber, M.D., Suzanne L. Topalian, M.D., Seth M. Steinberg, Ph.D., Helen X. Chen, M.D., and Steven A. Rosenberg, M.D., Ph.D.

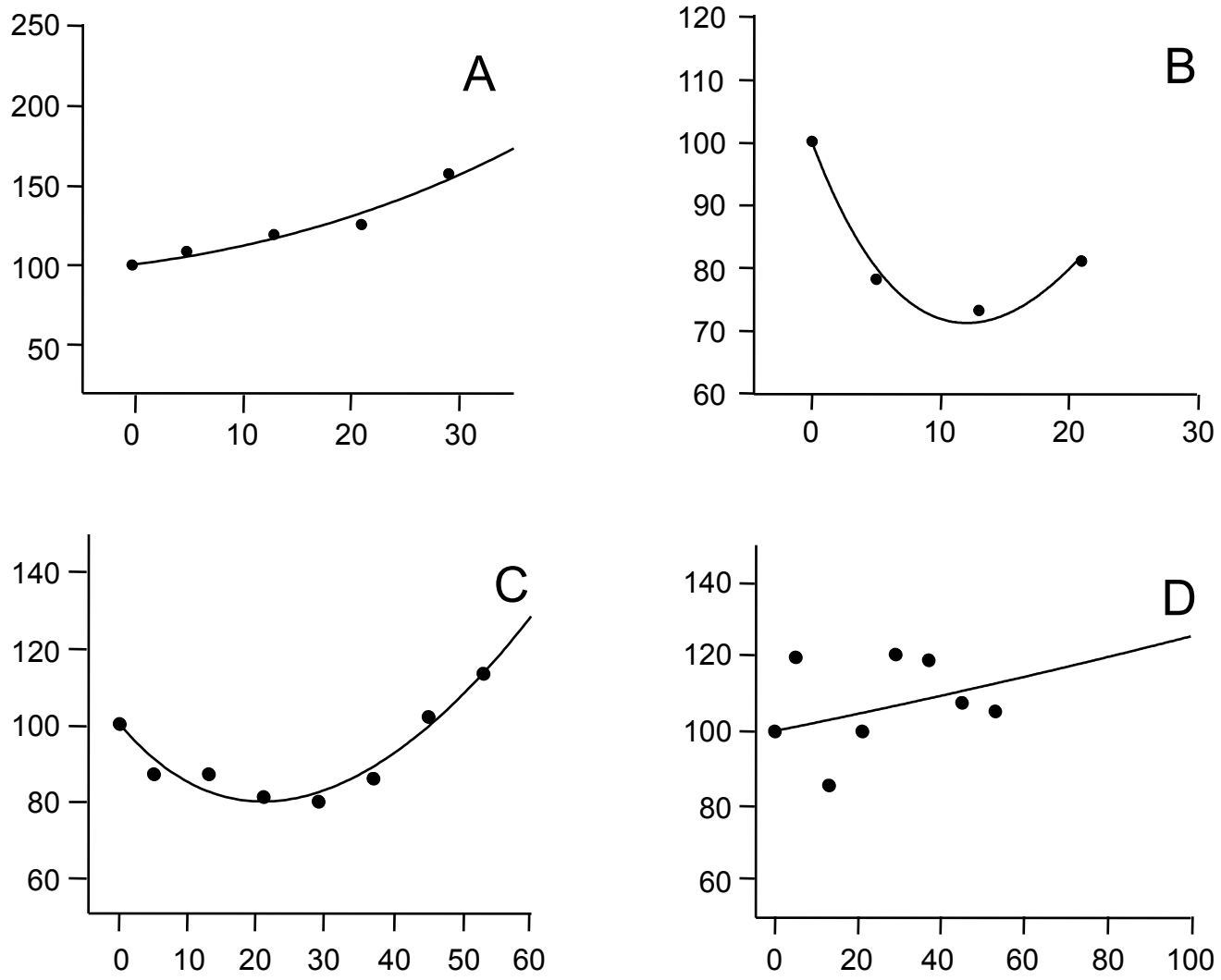


© 2012 American Association for Cancer Research

Kaplan-Meier Plot: Progression-Free Survival High-Dose Bevacizumab in Renal Cell Carcinoma



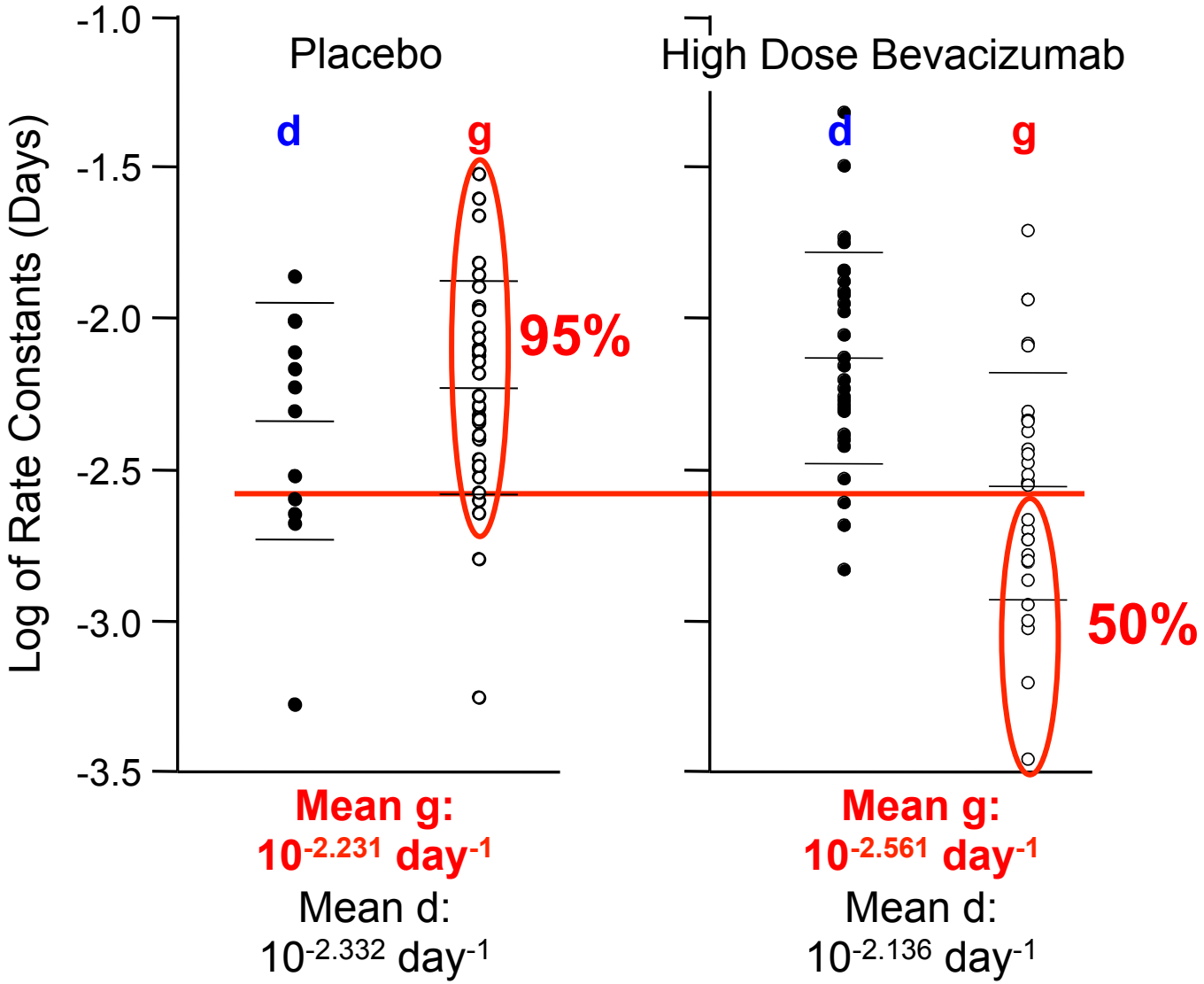
Curve Fits: Renal Cell Carcinoma. Bevacizumab Trial



$$f = e^{(-d \cdot t)} + e^{(g \cdot t)} - 1$$

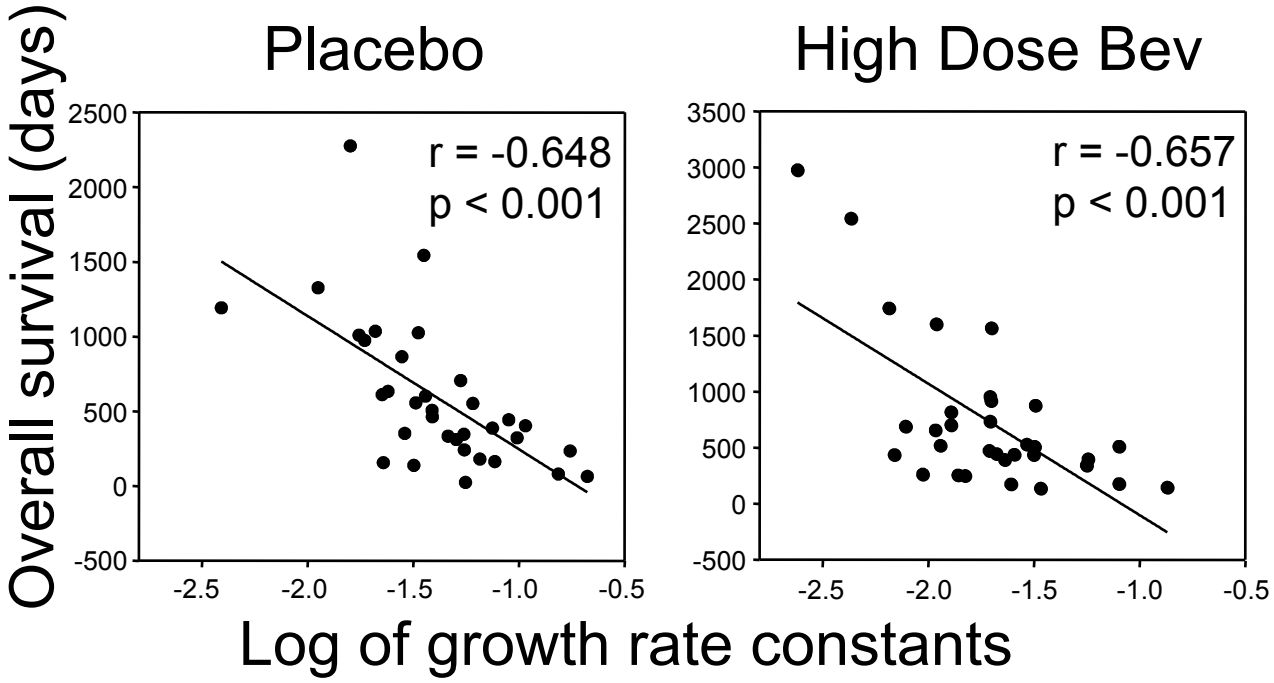
d = regression rate constant; g = growth rate constant

Dot Plot of Regression and Growth Rate Constants
Bevacizumab reduced the growth rate constant



Regression rate constants (●) / Growth rate constants (○) / Horizontal lines are mean ± SD

Growth Rates Correlate with Overall Survival in Renal Cell Carcinoma



The growth rate constant, g, is thus an excellent surrogate for the FDA gold standard – Overall Survival – and can help us discern effective therapies

Prostate Cancer

Patients with metastatic CRPC

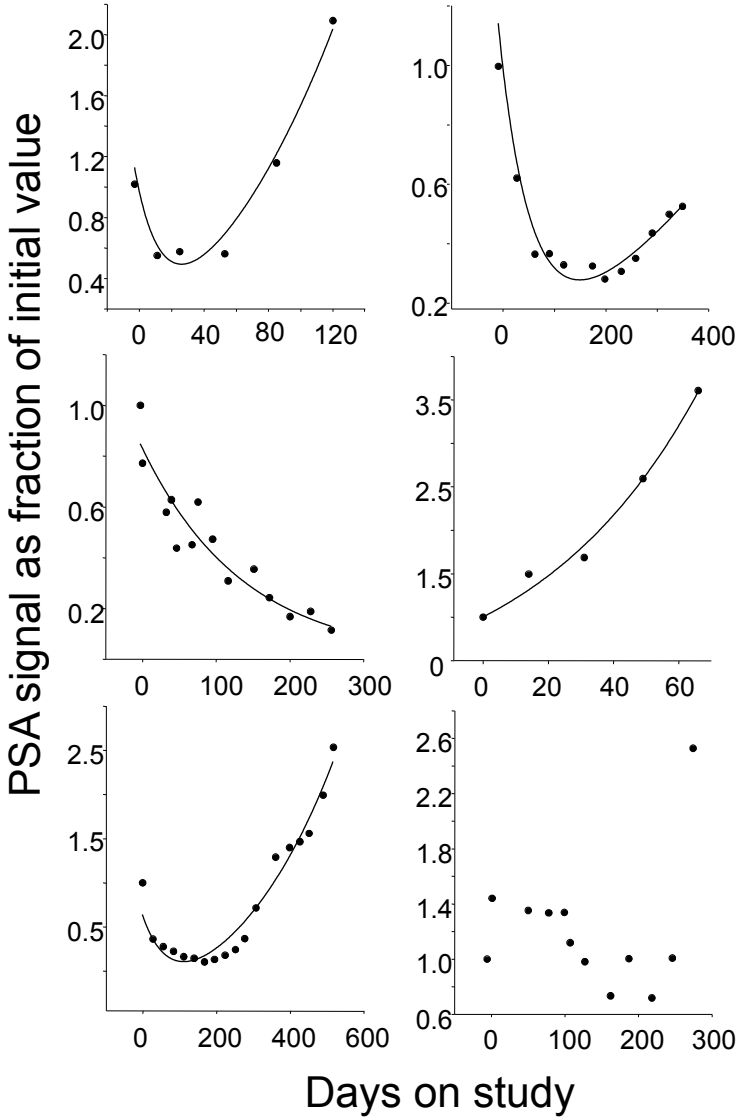
Did not benefit from:

1. Combined androgen blockade
2. Anti-androgen withdrawal

Chemotherapy:

1. Thalidomide
2. Docetaxel + Thalidomide
3. Ketoconazole + Alendronate
4. ATTP (Avastin + Thalidomide + Taxotere + Prednisone)

Curve Fits: Prostate Cancer



$$f = e^{(-d \cdot t)} + e^{(g \cdot t)} - 1$$

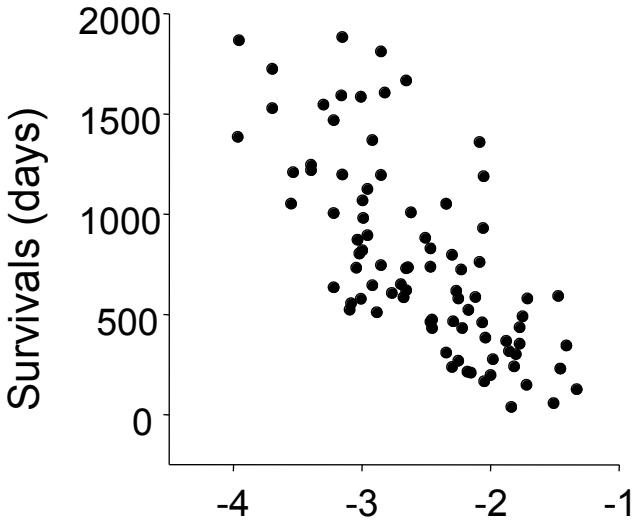
d = regression rate constant; g = growth rate constant

Prostate Cancer: Correlation of Parameters with Survival

Growth Rate

CORRELATES WITH SURVIVAL

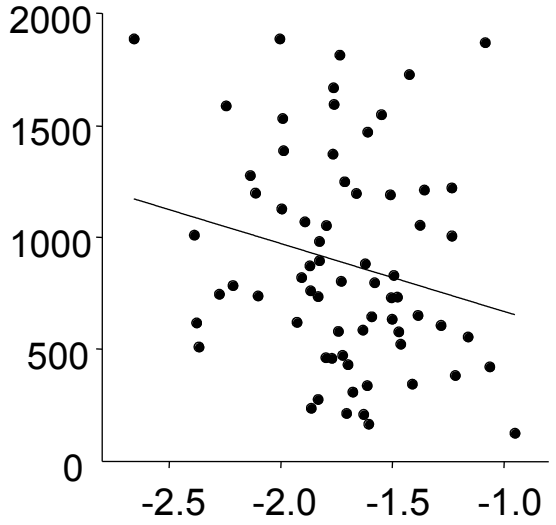
r = -0.72; p = < 0.0001



Regression Rate

NO CORRELATION WITH SURVIVAL

r = -0.218; p = < 0.074



Initial PSA

r = -0.22; p = < 0.0257

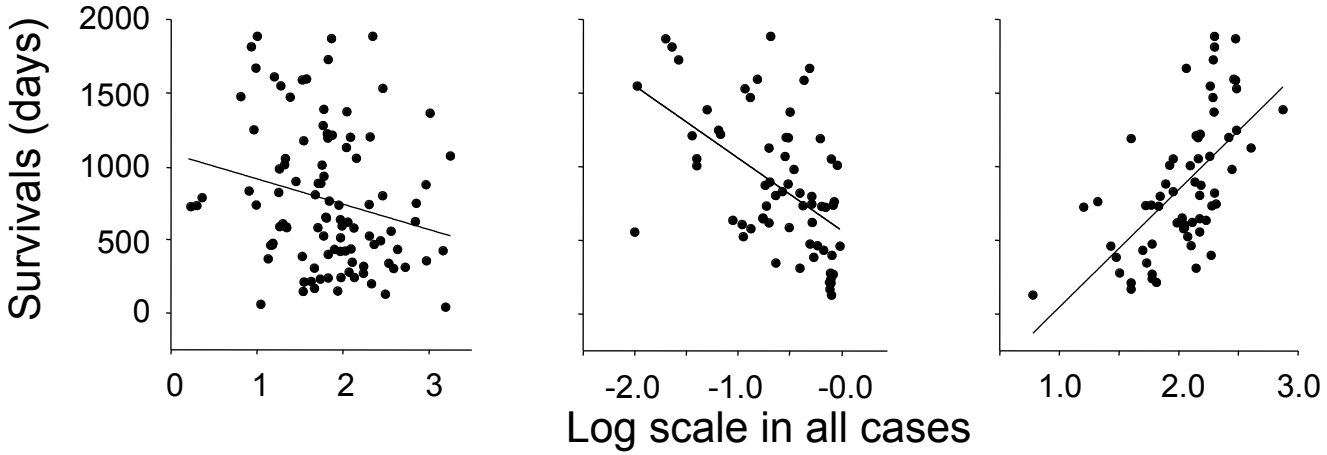
Minimum

r = -0.54; p = < 0.0001

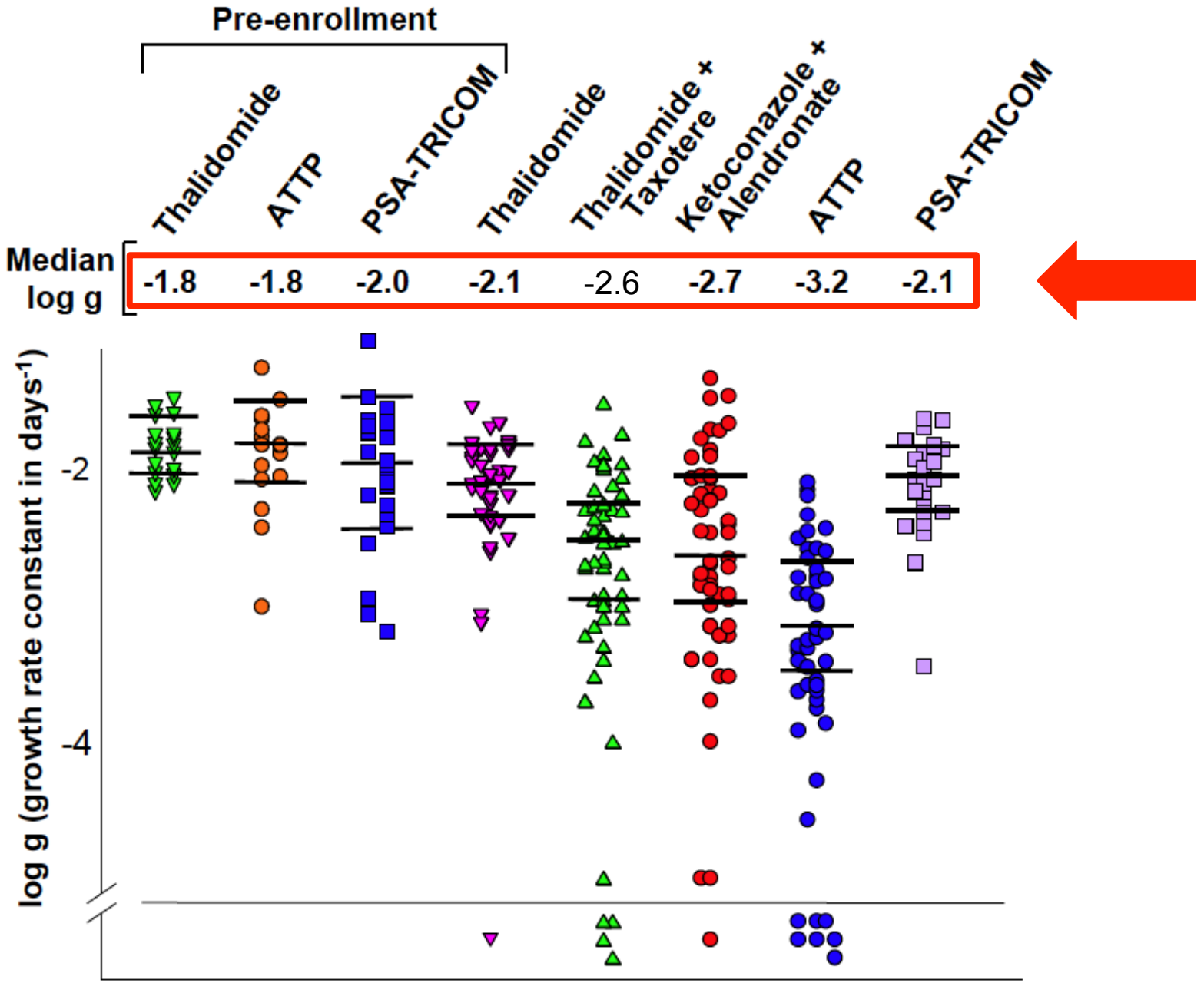
Time to Minimum

r = -0.62; p = < 0.0001

ALL CORRELATE WITH SURVIVAL – THEY ARE SURROGATES FOR g



12 Years of Prostate Cancer Trials at the NCI



Sunitinib

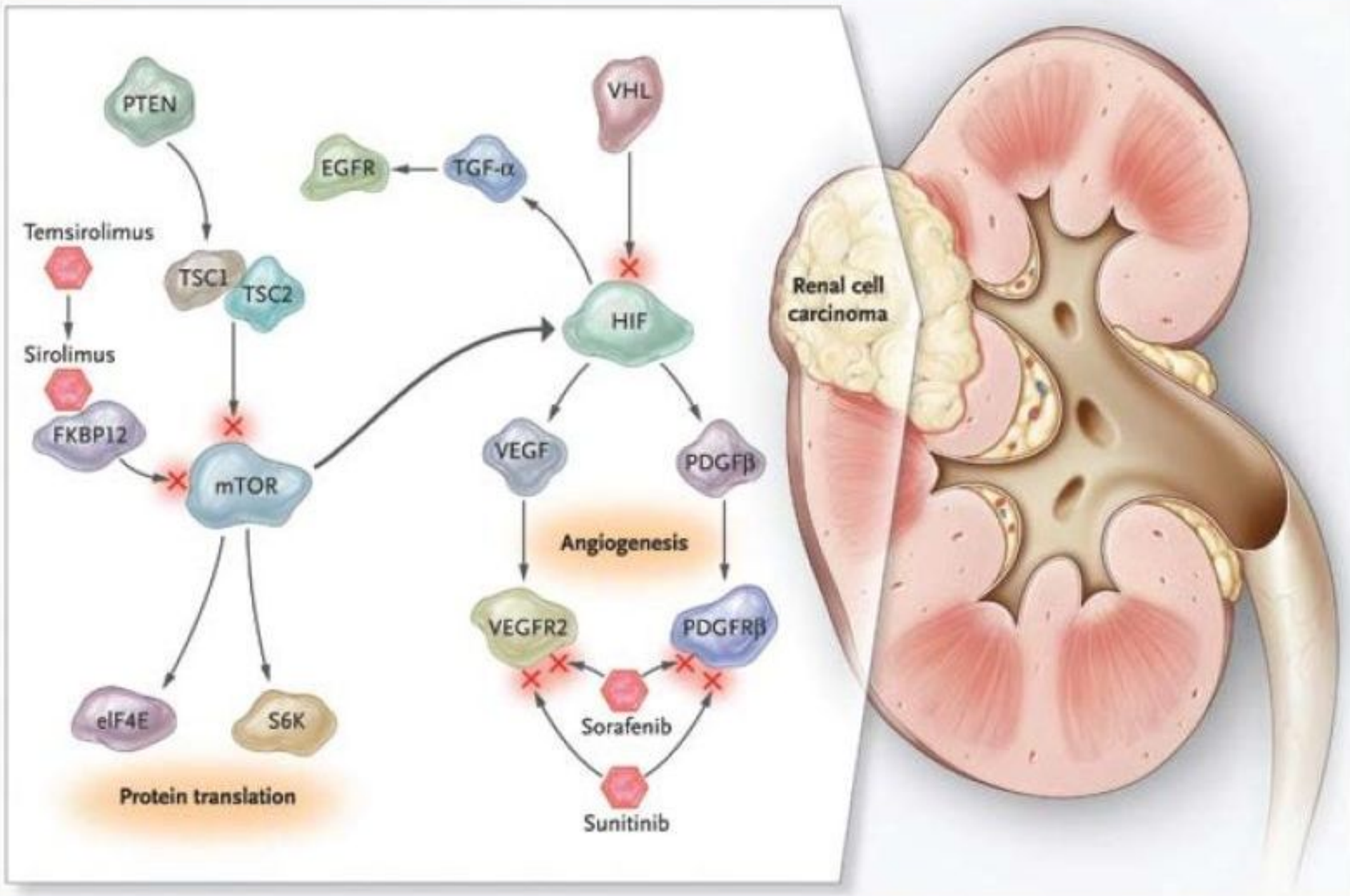
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 11, 2007 VOL. 356 NO. 2

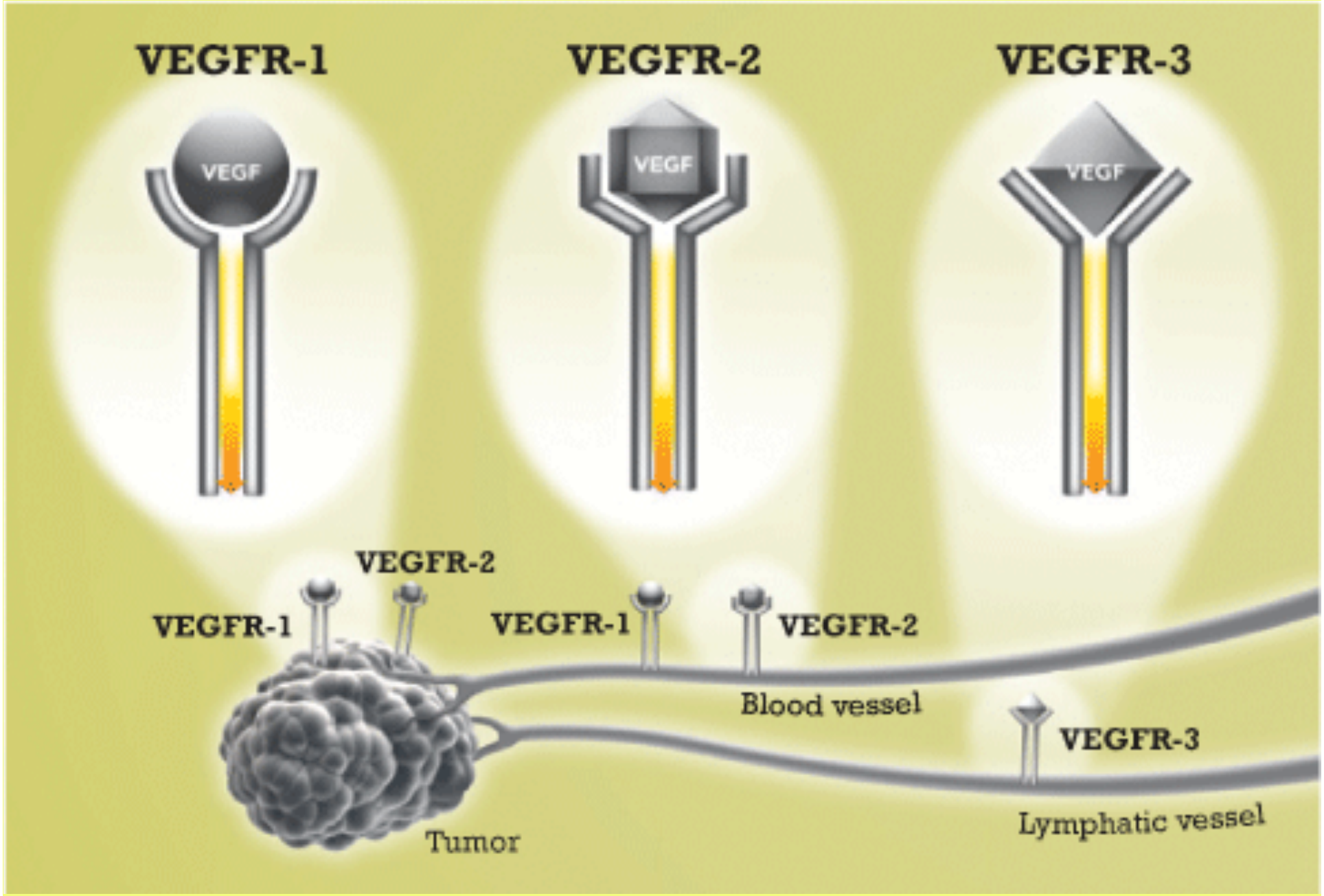
Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma

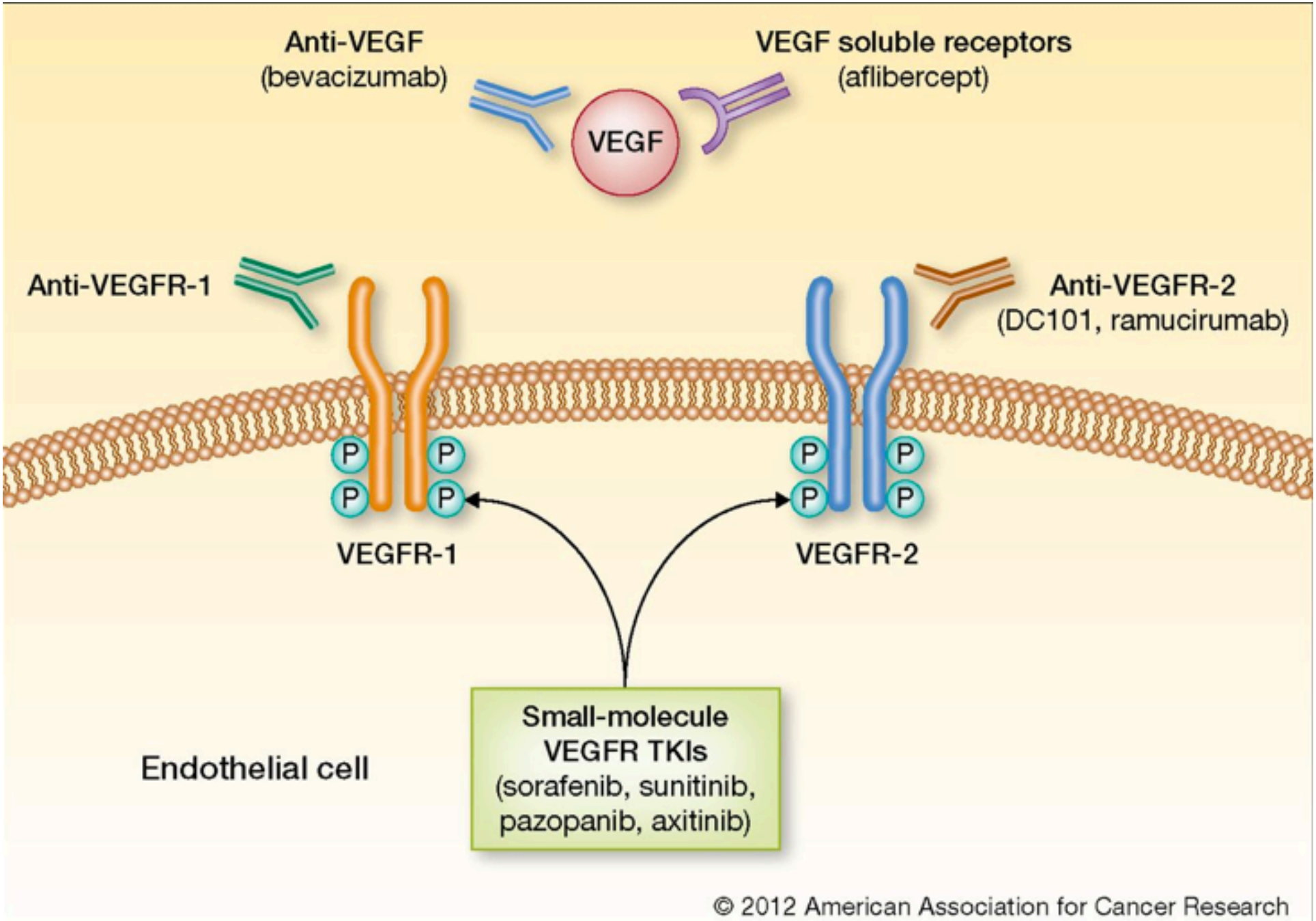
Robert J. Motzer, M.D., Thomas E. Hutson, D.O., Pharm.D., Piotr Tomczak, M.D., M. Dror Michaelson, M.D., Ph.D., Ronald M. Bukowski, M.D., Olivier Rixe, M.D., Ph.D., Stéphane Oudard, M.D., Ph.D., Sylvie Negrier, M.D., Ph.D., Cezary Szczylik, M.D., Ph.D., Sindy T. Kim, B.S., Isan Chen, M.D., Paul W. Bycott, Dr.P.H., Charles M. Baum, M.D., Ph.D., and Robert A. Figlin, M.D.*

Motzer NEJM 356: 115-124 (2007)



Source: Am J Health-Syst Pharm © 2009 American Society of Health-System Pharmacists


VEGFR-1
VEGFR-2
VEGFR-3
VEGF
VEGF
VEGF
VEGFR-2
VEGFR-1
VEGFR-1
VEGFR-2
Blood vessel
VEGFR-3
Lymphatic vessel
Tumor



© 2012 American Association for Cancer Research

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 11, 2007 VOL. 356 NO. 2

Sunitinib versus Interferon Alfa in Metastatic Renal-Cell Carcinoma

Robert J. Motzer, M.D., Thomas E. Hutson, D.O., Pharm.D., Piotr Tomczak, M.D., M. Dror Michaelson, M.D., Ph.D., Ronald M. Bukowski, M.D., Olivier Rixe, M.D., Ph.D., Stéphane Oudard, M.D., Ph.D., Sylvie Negrier, M.D., Ph.D., Cezary Szczylik, M.D., Ph.D., Sindy T. Kim, B.S., Isan Chen, M.D., Paul W. Bycott, Dr.P.H., Charles M. Baum, M.D., Ph.D., and Robert A. Figlin, M.D.*

VOLUME 27 · NUMBER 22 · AUGUST 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Overall Survival and Updated Results for Sunitinib Compared With Interferon Alfa in Patients With Metastatic Renal Cell Carcinoma

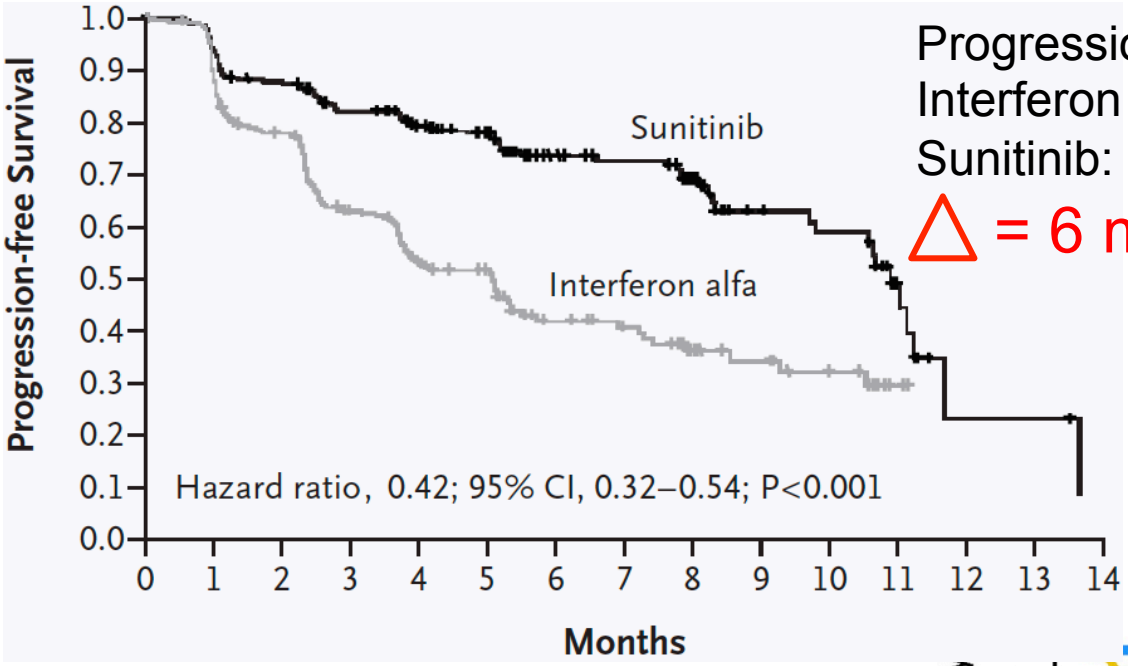
Robert J. Motzer, Thomas E. Hutson, Piotr Tomczak, M. Dror Michaelson, Ronald M. Bukowski, Stéphane Oudard, Sylvie Negrier, Cezary Szczylik, Roberto Pili, Georg A. Bjarnason, Xavier Garcia-del-Muro, Jeffrey A. Sosman, Ewa Solska, George Wilding, John A. Thompson, Sindy T. Kim, Isan Chen, Xin Huang, and Robert A. Figlin

Table 2. Best Tumor Response and Progression-Free Survival

Response	Sunitinib (n = 375) No. of Patients	Sunitinib (n = 375) %	IFN-α (n = 375) No. of Patients	IFN-α (n = 375) %
Objective response*	176	47	46	12
Complete response	11	3	4	1
Partial response	165	44	42	11
Stable disease	150	40	202	54
Progressive disease	26	7	69	18
Disease could not be evaluated or data missing	23	6	58	15
Progression-free survival†				
Patients in analysis	375		375	
Median, months	11		5	
95% CI, months	11 to 13		4 to 6	

Motzer R J et al. JCO 2009;27:3584-3590

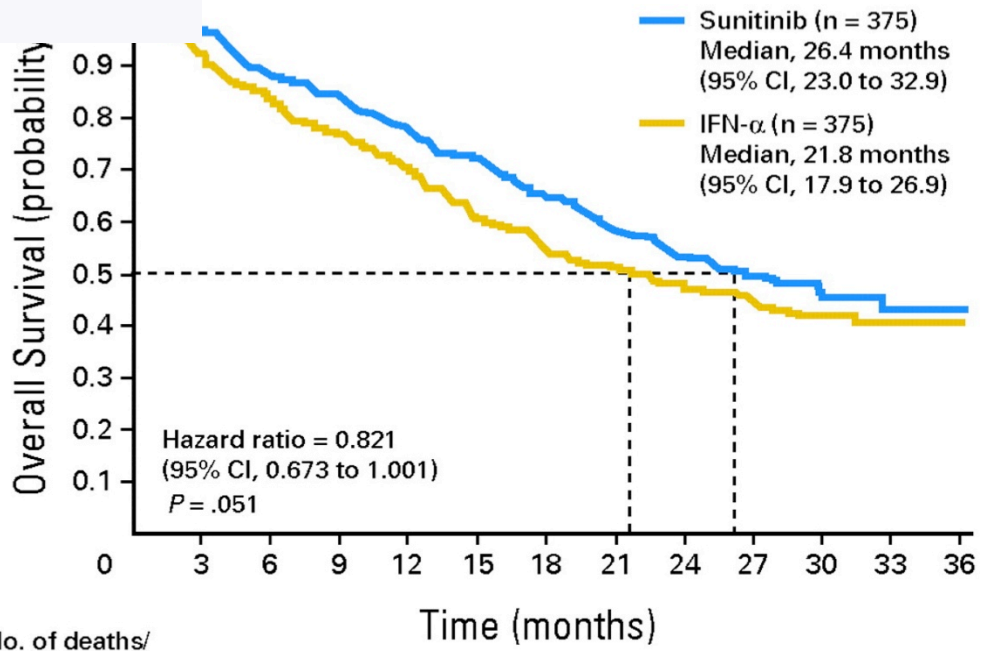
Progression-free and Overall Survival



Progression-free survival:
Interferon 5 months
Sunitinib: 11 months

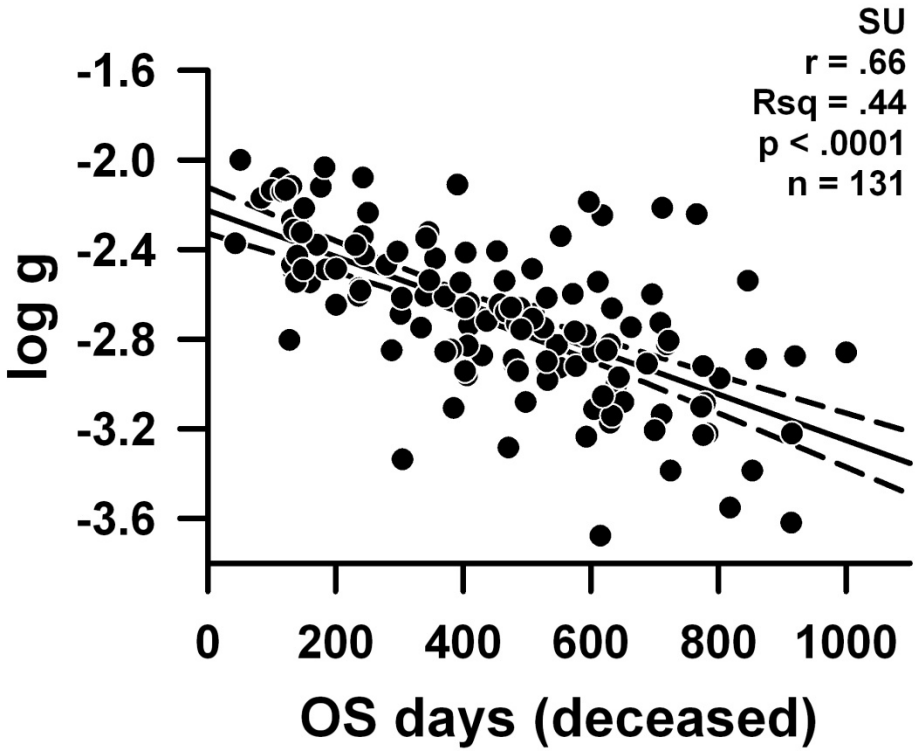
△ = 6 months

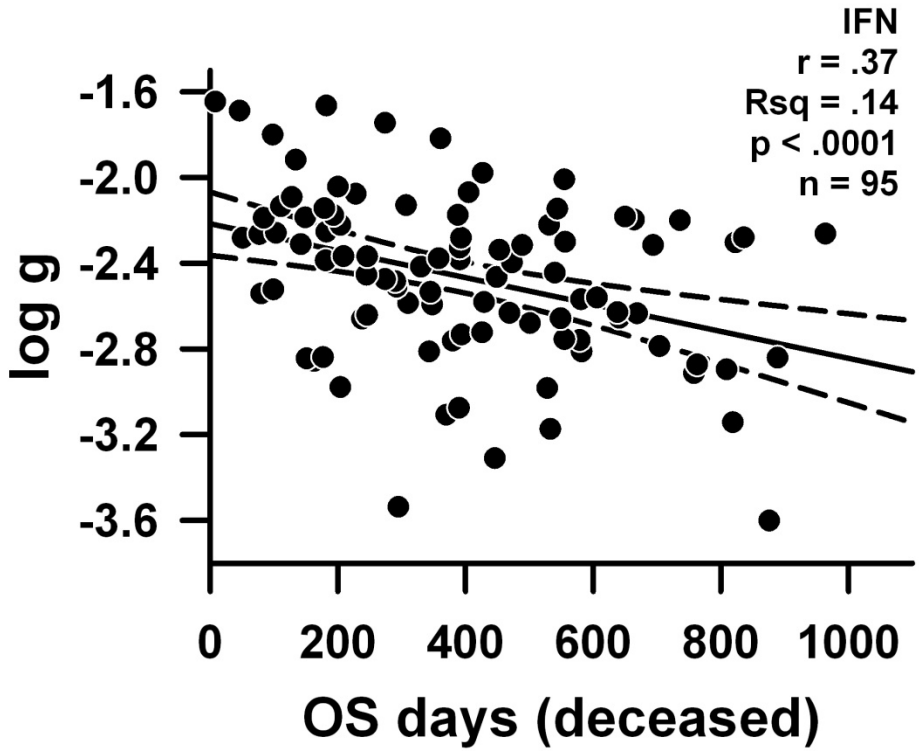
△ = 4.6 months



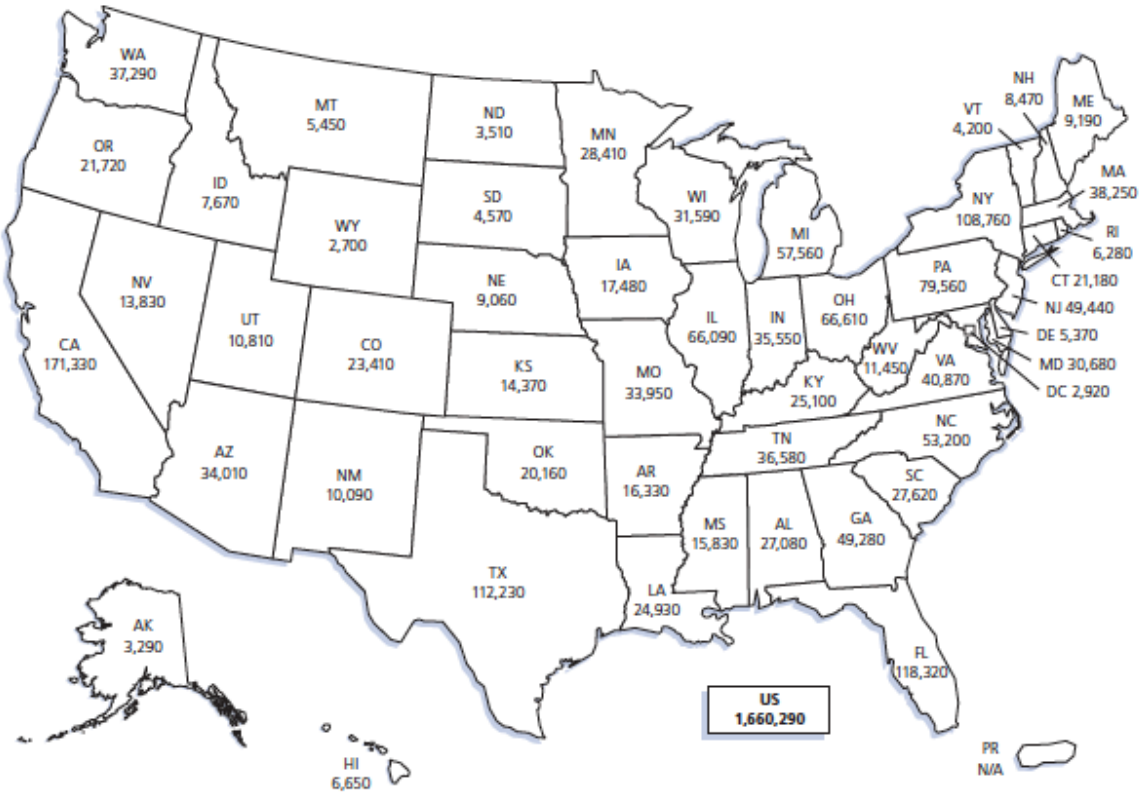
Motzer R J et al. JCO 2009;27:3584-3590

Log g correlates with overall survival
Especially in patients treated with sunitinib





Cancer Facts & Figures 2013



Estimated numbers of new cancer cases for 2013, excluding basal cell and squamous cell skin cancers and in situ carcinomas except urinary bladder.
Note: State estimates are offered as a rough guide and should be interpreted with caution. State estimates may not add to US total due to rounding.

Estimated Number* of New Cancer Cases and Deaths by Sex, US, 2013

	Estimated New Cases			Estimated Deaths		
	Both Sexes	**Male**	**Female**	**Both Sexes**	**Male**	**Female**
All Sites	1,660,290	854,790	805,500	580,350	306,920	273,430
Oral cavity & pharynx	41,380	29,620	11,760	7,890	5,500	2,390
Tongue	13,590	9,900	3,690	2,070	1,380	690
Mouth	11,400	6,730	4,670	1,800	1,080	720
Pharynx	13,930	11,200	2,730	2,400	1,790	610
Other oral cavity	2,460	1,790	670	1,640	1,260	380
Digestive system	290,200	160,750	129,450	144,570	82,700	61,870
Esophagus	17,990	14,440	3,550	15,210	12,220	2,990
Stomach	21,600	13,230	8,370	10,990	6,740	4,250
Small intestine	8,810	4,670	4,140	1,170	610	560
Colon†	102,480	50,090	52,390	50,830	26,300	24,530
Rectum	40,340	23,590	16,750			
Anus, anal canal, & anorectum	7,060	2,630	4,430	880	330	550
Liver & intrahepatic bile duct	30,640	22,720	7,920	21,670	14,890	6,780
Gallbladder & other biliary	10,310	4,740	5,570	3,230	1,260	1,970
Pancreas	45,220	22,740	22,480	38,460	19,480	18,980
Other digestive organs	5,750	1,900	3,850	2,130	870	1,260
Respiratory system	246,210	131,760	114,450	163,890	90,600	73,290
Larynx	12,260	9,680	2,580	3,630	2,860	770
Lung & bronchus	228,190	118,080	110,110	159,480	87,260	72,220
Other respiratory organs	5,760	4,000	1,760	780	480	300
Bones & joints	3,010	1,680	1,330	1,440	810	630
Soft tissue (including heart)	11,410	6,290	5,120	4,390	2,500	1,890
Skin (excluding basal & squamous)	82,770	48,660	34,110	12,650	8,560	4,090
Melanoma-skin	76,690	45,060	31,630	9,480	6,280	3,200
Other nonepithelial skin	6,080	3,600	2,480	3,170	2,280	890
Breast	234,580	2,240	232,340	40,030	410	39,620
Genital system	339,810	248,080	91,730	58,480	30,400	28,080
Uterine cervix	12,340		12,340	4,030		4,030
Uterine corpus	49,560		49,560	8,190		8,190
Ovary	22,240		22,240	14,030		14,030
Vulva	4,700		4,700	990		990
Vagina & other genital, female	2,890		2,890	840		840
Prostate	238,590	238,590		29,720	29,720	
Testis	7,920	7,920		370	370	
Penis & other genital, male	1,570	1,570		310	310	
Urinary system	140,430	96,800	43,630	29,790	20,120	9,670
Urinary bladder	72,570	54,610	17,960	15,210	10,820	4,390
Kidney & renal pelvis	65,150	40,430	24,720	13,680	8,780	4,900
Ureter & other urinary organs	2,710	1,760	950	900	520	380
Eye & orbit	2,800	1,490	1,310	320	120	200
Brain & other nervous system	23,130	12,770	10,360	14,080	7,930	6,150
Endocrine system	62,710	16,210	46,500	2,770	1,270	1,500
Thyroid	60,220	14,910	45,310	1,850	810	1,040
Other endocrine	2,490	1,300	1,190	920	460	460
Lymphoma	79,030	42,670	36,360	20,200	11,250	8,950
Hodgkin lymphoma	9,290	5,070	4,220	1,180	660	520
Non-Hodgkin lymphoma	69,740	37,600	32,140	19,020	10,590	8,430
Myeloma	22,350	12,440	9,910	10,710	6,070	4,640
Leukemia	48,610	27,880	20,730	23,720	13,660	10,060
Acute lymphocytic leukemia	6,070	3,350	2,720	1,430	820	610
Chronic lymphocytic leukemia	15,680	9,720	5,960	4,580	2,750	1,830
Acute myeloid leukemia	14,590	7,820	6,770	10,370	5,930	4,440
Chronic myeloid leukemia	5,920	3,420	2,500	610	340	270
Other leukemia*	6,350	3,570	2,780	6,730	3,820	2,910
Other & unspecified primary sites*	31,860	15,450	16,410	45,420	25,020	20,400

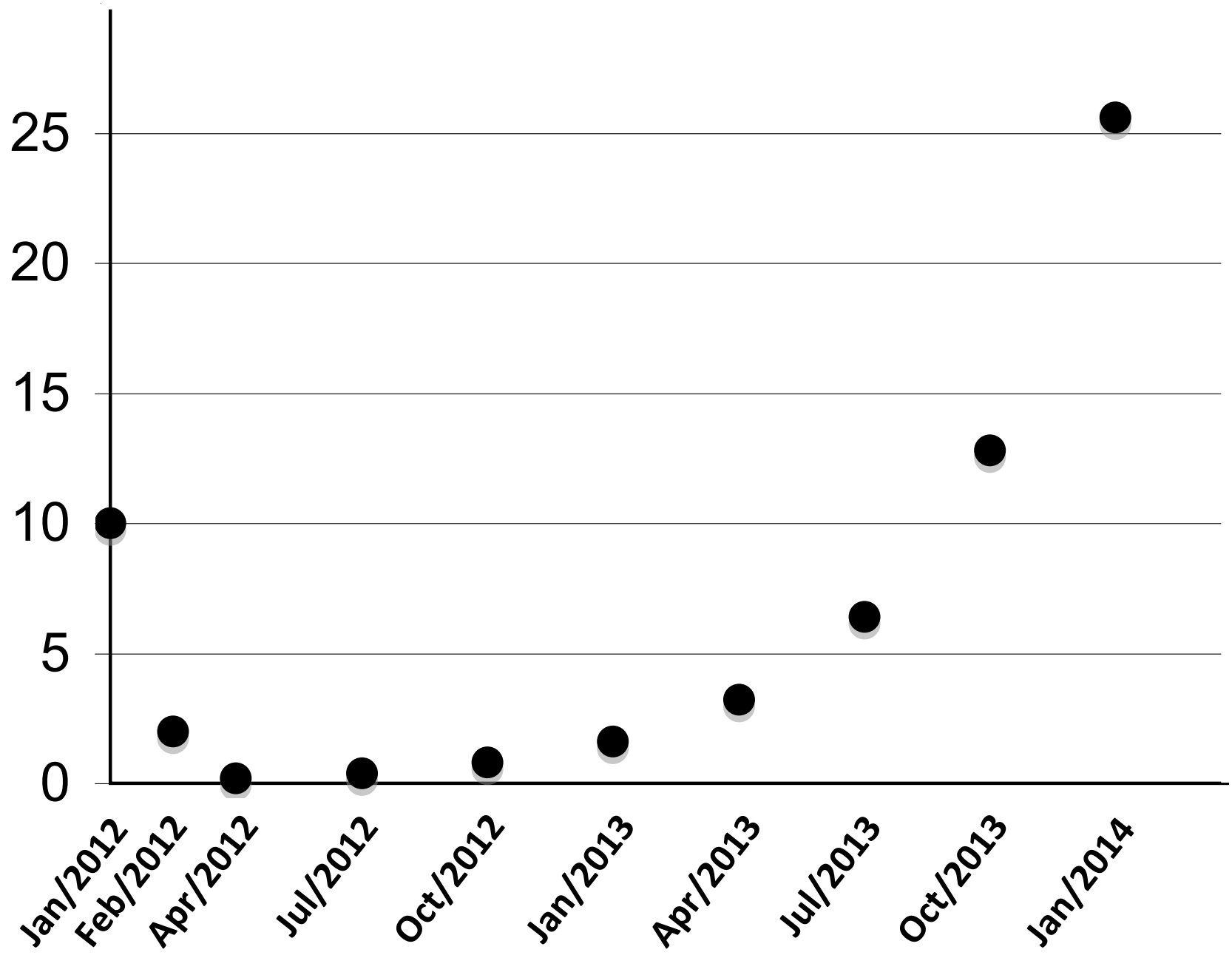
Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial

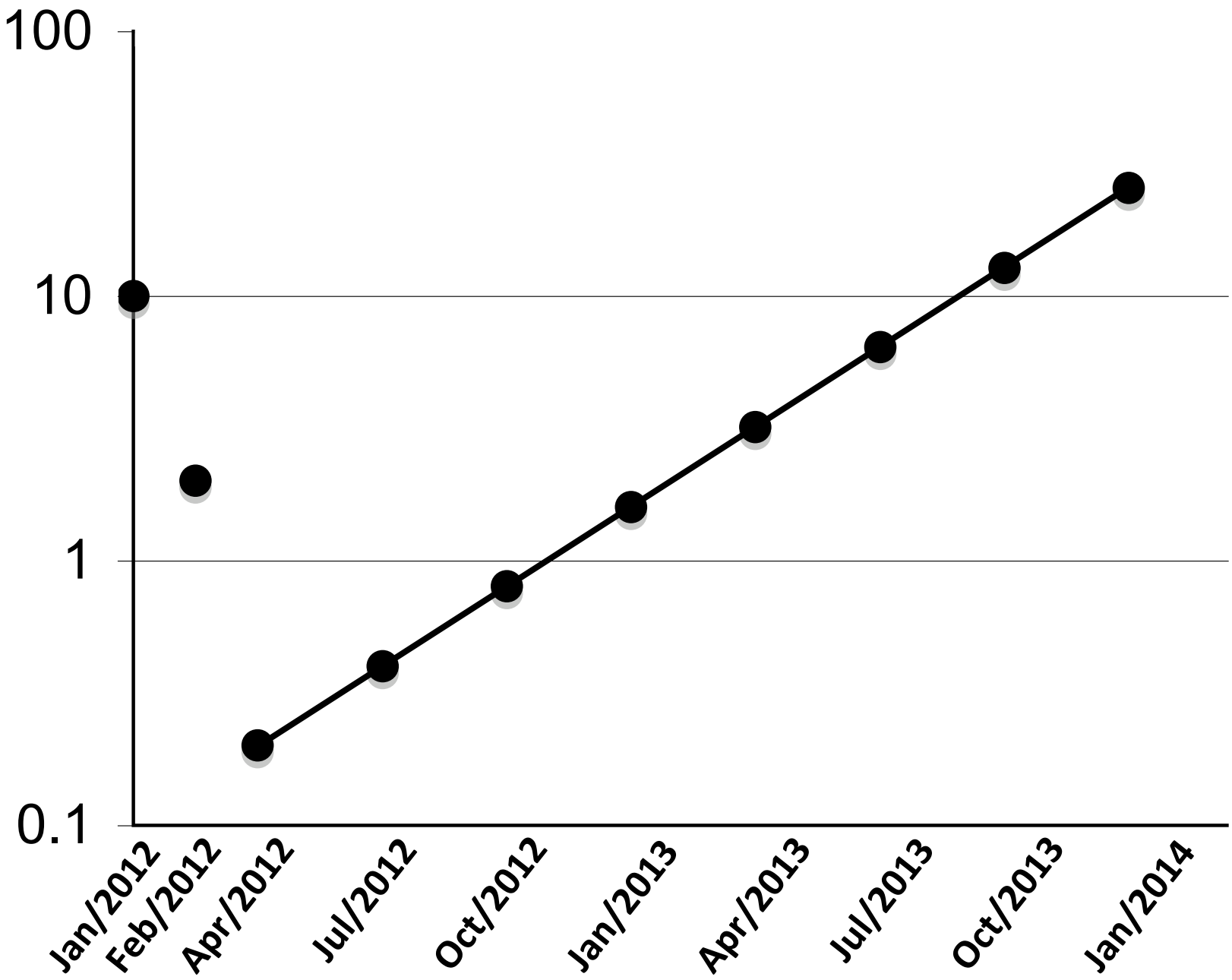
Brian I Rini, Bernard Escudier, Piotr Tomczak, Andrey Kaprin, Cezary Szczylik, Thomas E Hutson, M Dror Michaelson, Vera A Gorbunova, Martin E Gore, Igor G Rusakov, Sylvie Negrier, Yen-Chuan Ou, Daniel Castellano, Ho Yeong Lim, Hirotsugu Uemura, Jamal Tarazi, David Cella, Connie Chen, Brad Rosbrook, Sinil Kim, Robert J Motzer

Rini et al, Lancet 378:1931-1939 (2011)

Patient with prostate cancer

	PSA	
January 2012:	**10**	**Start chemotherapy?**
Mid-February 2012:	**2**	**Continue chemotherapy?**
April 2012:	**0.2**	**Continue chemotherapy?**
July 2012:	**0.4**	**Continue chemotherapy?**
October 2012:	**0.8**	**Continue chemotherapy?**
January 2013:	**1.6**	**Continue chemotherapy?**
April 2013:	**3.2**	**Continue chemotherapy?**
July 2013:	**6.4**	**Continue chemotherapy?**
October 2013:	**12.8**	**Continue chemotherapy?**
January 2014:	**25.6**	**Continue chemotherapy?**


25
20
15
10
5
0
Jan/2012
Feb/2012
Apr/2012
Jul/2012
Oct/2012
Jan/2013
Apr/2013
Jul/2013
Oct/2013
Jan/2014


100
10
1
0.1
Jan/2012
Feb/2012
Apr/2012
Jul/2012
Oct/2012
Jan/2013
Apr/2013
Jul/2013
Oct/2013
Jan/2014

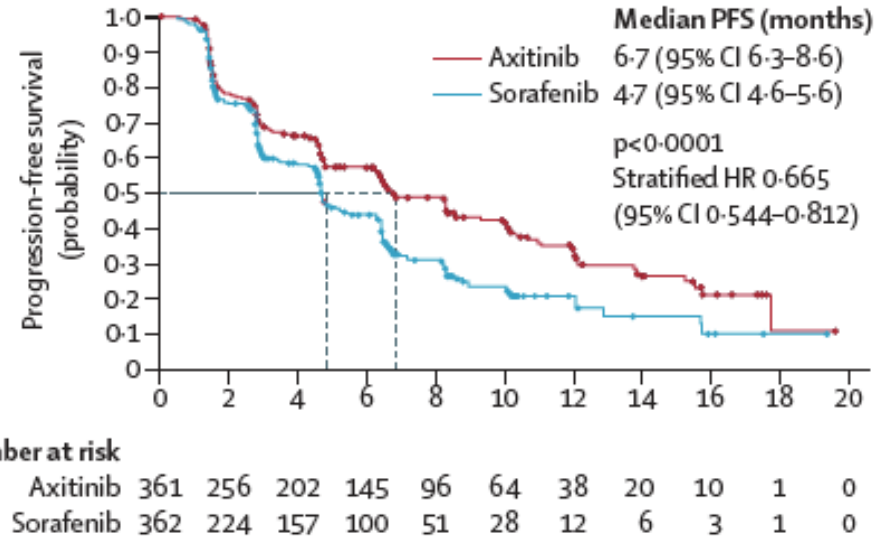
Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial

Brian I Rini, Bernard Escudier, Piotr Tomczak, Andrey Kaprin, Cezary Szczylik, Thomas E Hutson, M Dror Michaelson, Vera A Gorbunova, Martin E Gore, Igor G Rusakov, Sylvie Negrier, Yen-Chuan Ou, Daniel Castellano, Ho Yeong Lim, Hirotsugu Uemura, Jamal Tarazi, David Cella, Connie Chen, Brad Rosbrook, Sinil Kim, Robert J Motzer

Rini et al, Lancet 378:1931-1939 (2011)

Progression-free Survival

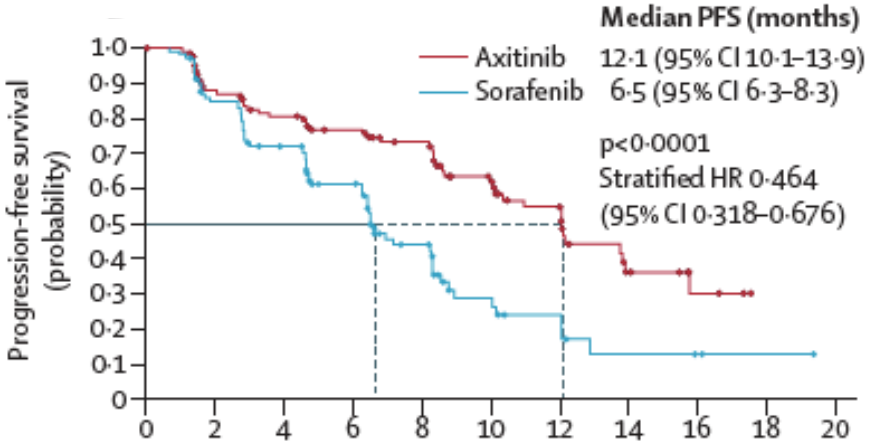
All patients



Number at risk

Axitinib	361	256	202	145	96	64	38	20	10	1	0
Sorafenib	362	224	157	100	51	28	12	6	3	1	0

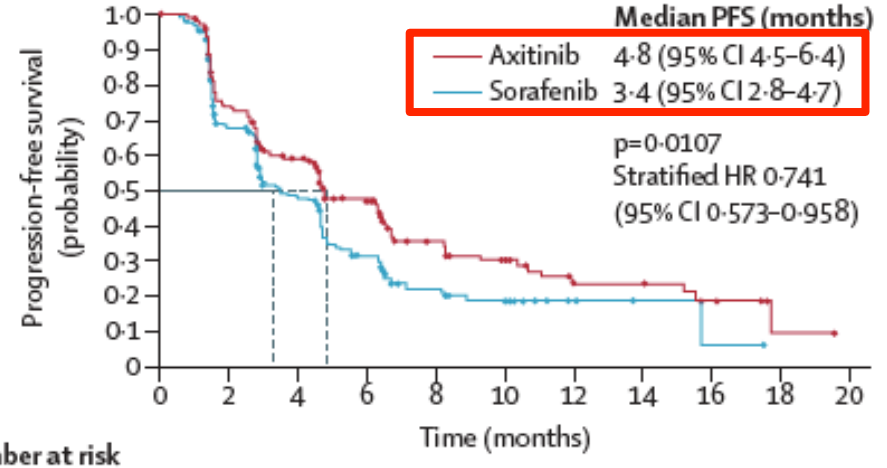
Prior Cytokine



Number at risk

Axitinib	126	98	86	73	55	38	27	10	4	0	0
Sorafenib	125	93	75	57	28	12	7	3	2	1	0

Prior Sunitinib

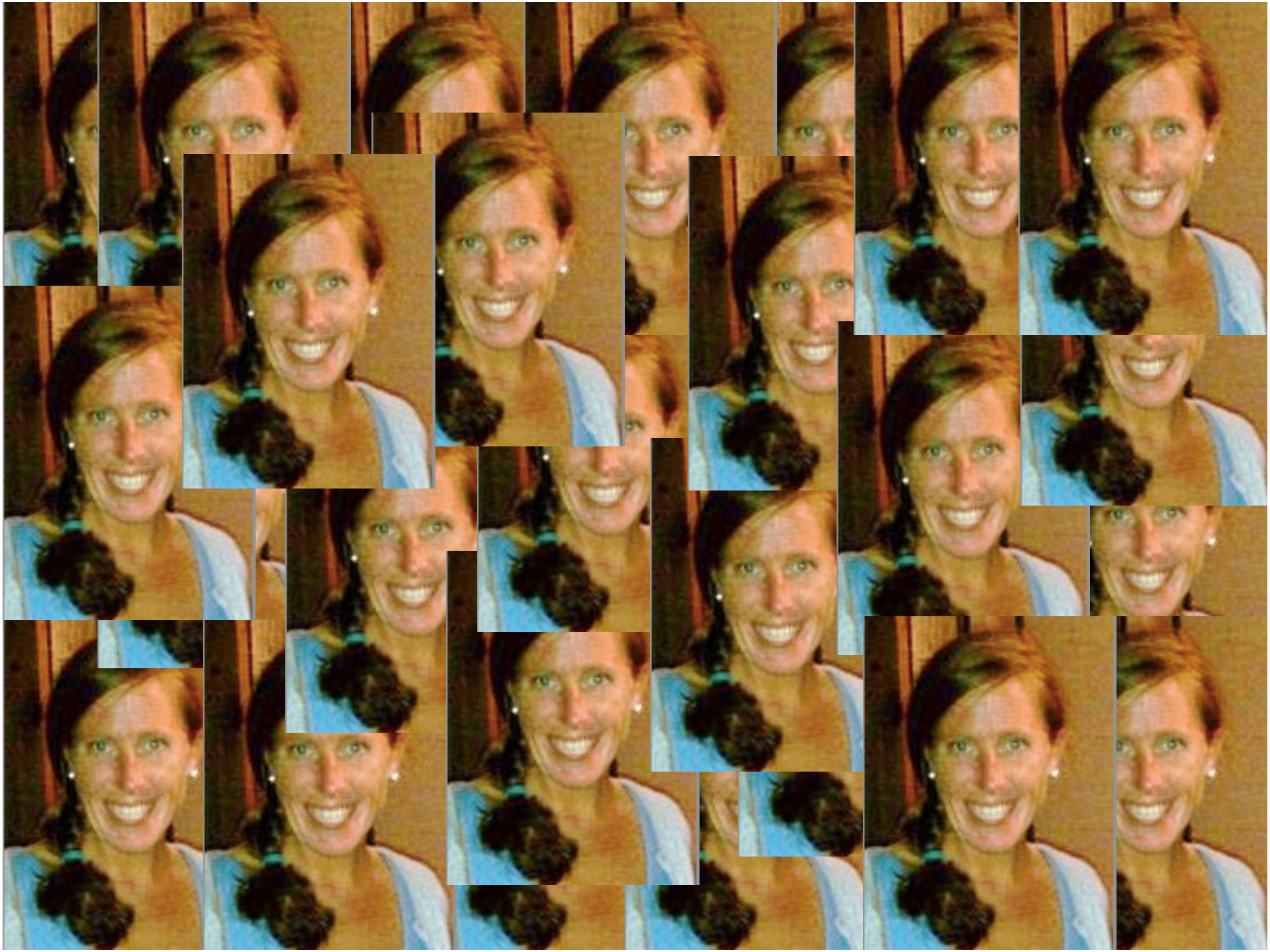


Number at risk

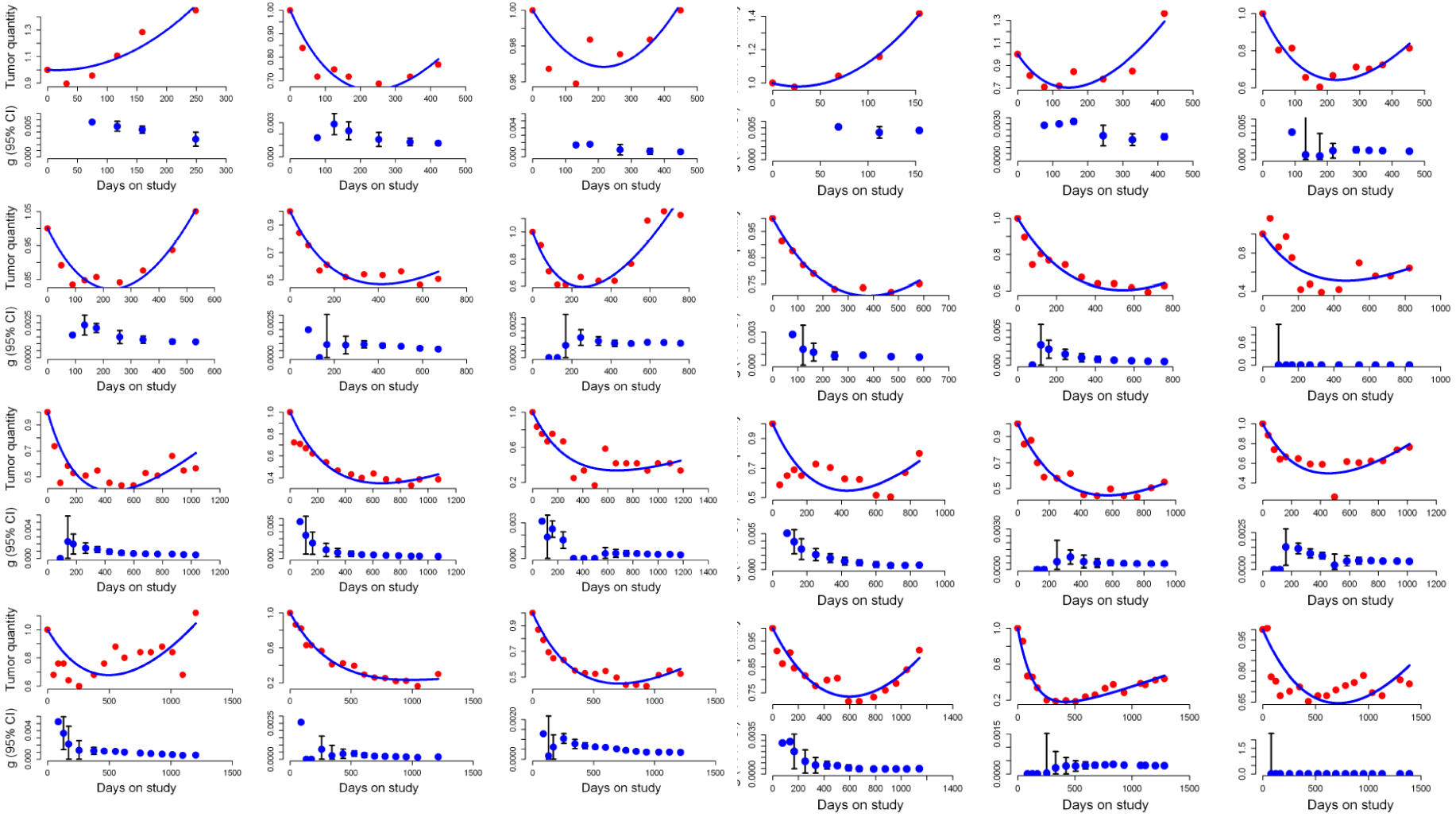
Axitinib	184	132	97	60	34	24	11	10	6	1	0
Sorafenib	185	104	67	37	20	13	5	3	1	0	0

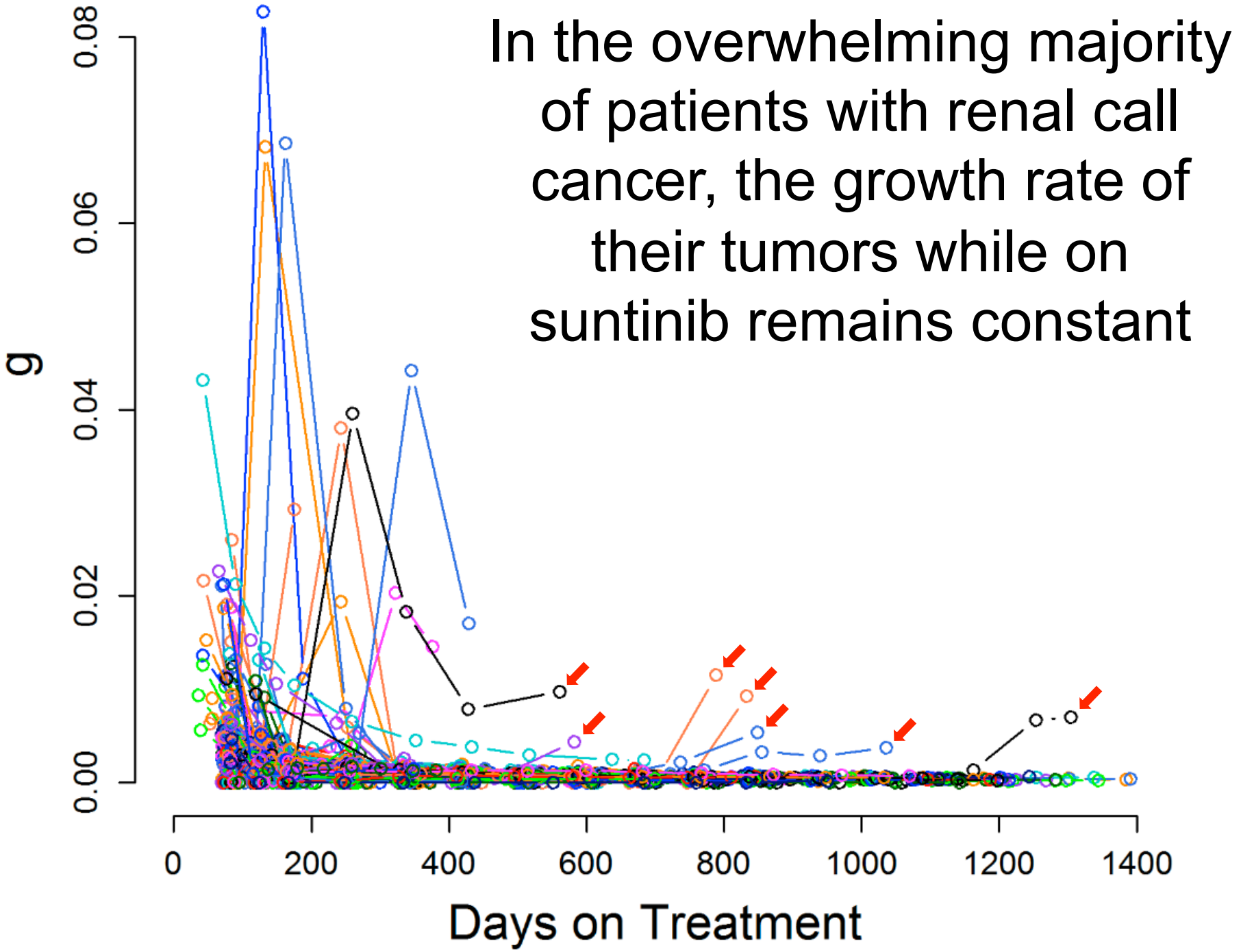
Rini et al, Lancet 378:1931-1939 (2011)

Julia Wilkerson



In the overwhelming majority of patients with renal call cancer, the growth rate of their tumors while on suntinib remains constant




In the overwhelming majority of patients with renal call cancer, the growth rate of their tumors while on suntinib remains constant
g
0.00
0.02
0.04
0.06
0.08
0
200
400
600
800
1000
1200
1400
Days on Treatment

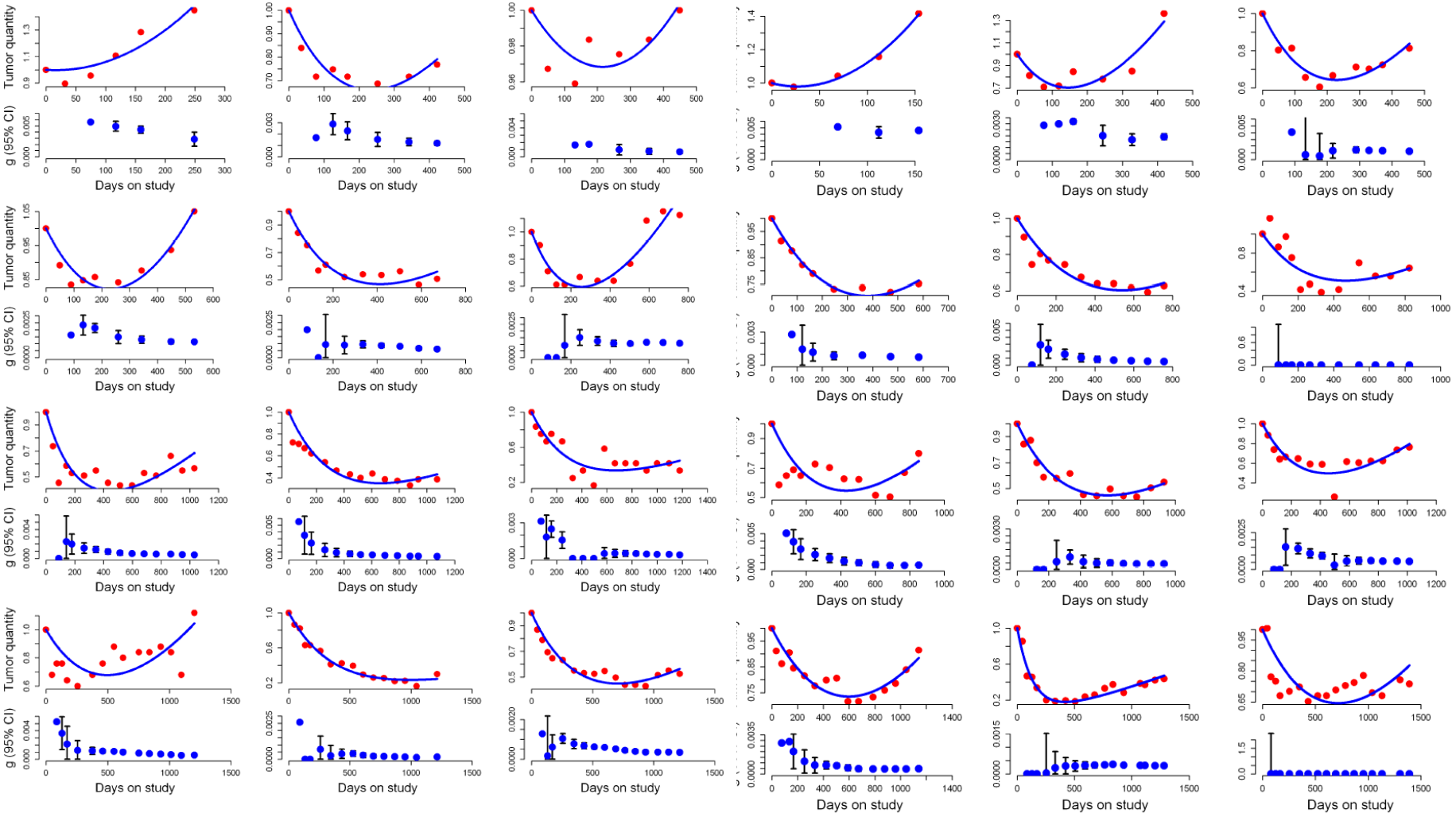
We can calculate the time to progression were sunitinib continued and compare this to approved therapies

$$\frac{\text{Ln } 1.2}{g} = \text{Time to PFS} \Rightarrow \frac{0.182}{0.00082} = 222 \text{ days (7.3 months)}$$

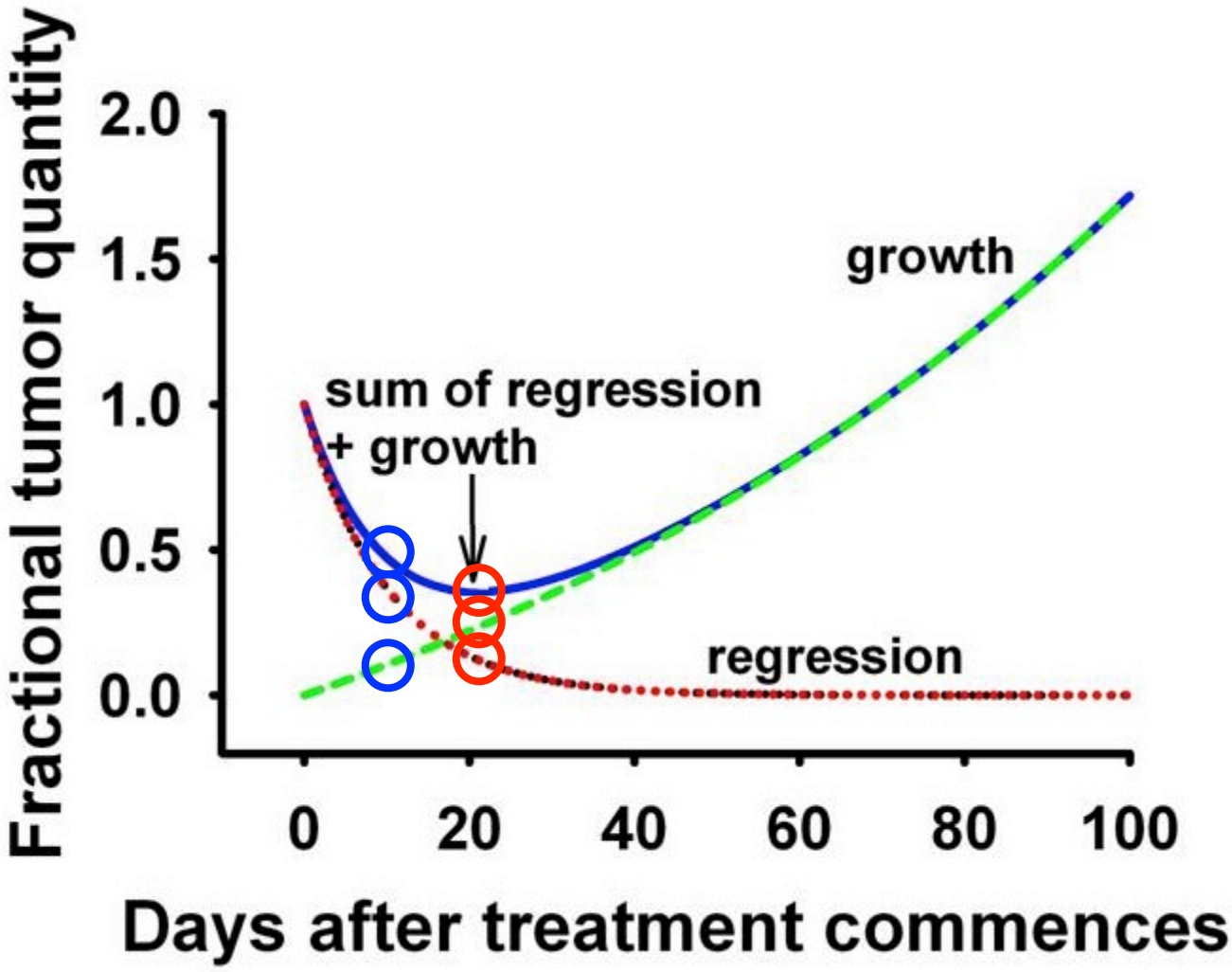
Reported Progression-free Survival [PFS] in second line in patients treated in first line with sunitinib

Drug	PFS	Author
Everolimus	3.9 months	Calvo 2012
Sorafenib	3.4 months	Rini 2011
Axitinib	4.8 months	Rini 2011
Sunitinib	7.3 months*	Burotto 2013

The constant growth rate of these renal cell carcinomas treated with suntinib suggest resistance is intrinsic and not acquired



Theory for regression and growth

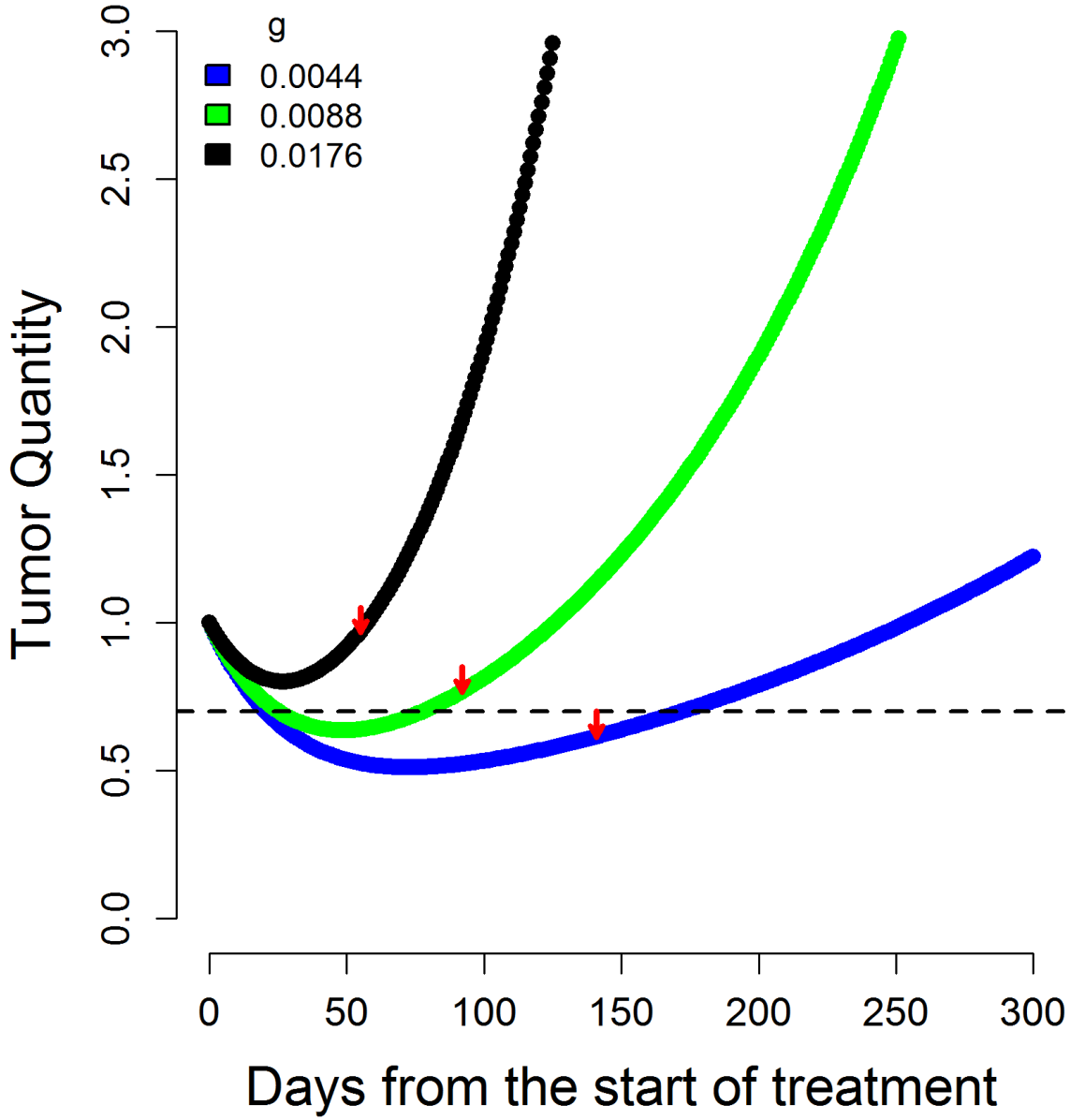


$$f = e^{(-d \cdot t)} + e^{(g \cdot t)} - 1$$

Where f = tumor measurement in t days

d = regression rate constant; g = growth rate constant

Slowing the growth rate without killing additional tumor can result in an ***apparent*** greater cell kill



We collect data and we ignore it.

But by looking deeper we now know that:

1. We should think of a tumor as a dynamic entity composed of a drug sensitive portion that is regressing and a drug resistant fraction that is growing
2. We can measure the rate of growth of the resistant fraction (g) and this correlates with overall survival
3. In a given patient the rate of growth of the tumor is as if not more important than the absolute quantity of tumor
4. The rate of tumor growth while on a therapy remains constant. It appears to have been constant from the outset suggesting drug resistance is intrinsic

5. The best thing one can do for a patient is continue a therapy on which the tumor is growing.
6. A higher response rate does not mean more tumor was killed by that the therapy that achieved this. This is most often achieved by reducing the rate of growth of the tumor. By reducing the rate of growth the sensitive tumor has more time to maximally regress.
7. Most of our therapies are “g” therapies meaning they only reduce the rate of tumor growth and do not kill more cancer cells.

Conclusions

1. Using data collected as part of a clinical trial we can calculate the rates of tumor growth and regression
2. These rates are constant as long as a therapy is administered
3. The rates of growth correlate well with overall survival
4. Estimating these rates can give us ways to assess tumor growth and better understand our therapies – in effect gather an enormous amount of data and analyze it
5. Estimating these rates can also give us insight into how we might alter therapies such as by continuing them for longer periods to achieve greater benefit

Acknowledgements

Tito Fojo
Wilfred Stein
Julia Wilkerson
Krastan Blagoev
Susan Bates
Sanjeeve Balasubramanian
Irfan Jawed
Nicolas Acquavella Pesantes
Maureen Edgerly
Lyn Huff
Jeff Schlom
Bill Dahut
Ravi Madan
James Gulley
Doug Figg
Doug Price
James Yang
Bob Motzer